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First Named Inventor	Joseph SYPEK
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Examiner Name	P. Gambel
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ENCLOSURES (*Check all that apply*)

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- [x] Other Enclosure(s) (please Identify below):

Appendix B (33 pgs), Appendix C (35 pgs)
Appendix D (36 pgs), Appendix E (6 pgs)
Appendix F (4 pgs), Appendix G (7 pgs)
Appendix H (7 pgs), Appendix I (10 pgs)
Appendix J (10 pgs), Appendix K (5 pgs)
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Firm Name	LAHIVE & COCKFIELD, LLP		
Signature			
Printed name	Cynthia L. Kanik, Ph.D.		
Date	April 15, 2005	Reg. No.	37,320

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Dated: April 15, 2005 Signature: _____ (Cynthia L. Kanik, Esq.)

Docket No. GNN-018CP
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Joseph Sypek, *et al.*

Serial No.: 09/805,800

Filed: March 13, 2001

For: *Use of Rapamycin and Agents That Inhibit B7 Activity in Immunomodulation*

Attorney Docket No.: GNN-018CP

Group Art Unit: 1644

Examiner: P. Gambel

MS Appeal Brief - Patents
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AMENDED APPEAL BRIEF

This Amended Appeal Brief is submitted in response to the Notification of Non-Compliant Appeal Brief mailed from the Patent Office March 18, 2005.

As indicated in the Notice of Appeal filed on June 4, 2004, Appellants hereby appeal the final decision of the Examiner in the above-identified application rejecting the subject matter of the pending claims. For the reasons set forth in this brief, Appellants respectfully request the Board of Patent Appeals and Interferences to reverse the Examiner's final rejection of the claimed subject matter.

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Genetics Institute, Inc.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellants, Appellants' legal representative, or the assignees which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 4, 5, and 7-13 are pending in this application. Claims 2, 3, and 6 have been previously canceled.

Claims 1, 4, 5, and 7-13 are on appeal and are set forth in the Claims Appendix (Appendix A).

IV. STATUS OF THE AMENDMENTS

A Notice of Appeal was filed on June 4, 2004. All prior amendments have been entered. A Request for an appropriate Extension of Time is being filed with this Appeal Brief.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The instant invention is based, at least in part, on the finding that agents that decrease co-stimulatory signals to T cells are more efficient in reducing symptoms of autoimmune disease when used in combination with Rapamycin or Rapamycin-like compounds. Accordingly, the invention provides improved methods of downmodulating immune responses by a cell expressing a B7 molecule with a combination of at least one antibody which binds to at least one B7 molecule and a Rapamycin compound (see, *e.g.*, page 5, lines 3-6).

One aspect of the invention provides a method for downmodulating an immune response comprising contacting immune cells from a subject with a Rapamycin compound in combination with at least two antibodies, wherein each of said antibodies binds to a different B7 molecule selected from the group consisting of B7-1, B7-2, B7-H1, or B7RP-1 (see, *e.g.*, page 5, lines 6-8). In one embodiment, the step of contacting is performed *in vivo* (see, *e.g.*, page 5, line 10).

In another aspect of the invention, a method for downmodulating an immune response in a subject having an autoimmune disorder is provided, comprising contacting immune cells from the subject with a Rapamycin compound in combination with at least two antibodies, wherein each of said antibodies binds to a different B7 molecule selected from the group consisting of B7-1, B7-2, B7-H1, or B7RP-1(see, *e.g.*, page 6, lines 8-10). In one embodiment, the autoimmune disorder is systemic lupus erythematosis (see, *e.g.*, page 5, lines 10-11).

In one aspect of the invention, a method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis is provided, comprising administering to the subject an antibody that binds to B7-1, an antibody that binds to B7-2, and a Rapamycin compound, wherein the antibody that binds to B7-1 and the antibody that binds to B7-2 are administered over at least one short course of therapy (see, *e.g.*, page 10, lines 26-28).

In another aspect of the invention, a method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis is provided, comprising administering to the subject an antibody that binds to B7-1, an antibody that binds to B7-2, and a Rapamycin compound, wherein the Rapamycin compound is administered over at least one intermediate course of therapy (see, *e.g.*, page 10, lines 28-32).

In yet another aspect of the invention, a method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis is provided, comprising administering to said subject an antibody that binds B7-1, an antibody that binds B7-2, and a Rapamycin compound, wherein said Rapamycin compound is administered over at least one extended course of therapy (see, *e.g.*, page 10, line 32, through page 11, lines 1-4).

In one aspect of the invention, a method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis is provided,

comprising administering to said subject an antibody that binds B7-1, an antibody that binds B7-2, and a Rapamycin compound, wherein said Rapamycin compound is administered according to an early dosing regimen (see, *e.g.*, page 11, lines 5-8).

In another aspect of the invention, a method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis is provided, comprising administering to said subject an antibody that binds B7-1, an antibody that binds B7-2, and a Rapamycin compound, wherein said Rapamycin compound is administered according to a late dosing regimen (see, *e.g.*, page 11, lines 8-10).

In one aspect, the invention provides a method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis comprising administering to said subject an antibody that binds B7-1, an antibody that binds B7-2, a Rapamycin compound, and an immunosuppressing agent, wherein said immunosuppressing agent is selected from the group consisting of FK506, Cyclosporine A and cyclophosphamide (see, *e.g.*, page 41, lines 15-18).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants present the following issues for review:

1. Whether claims, 1, 4, 5, and 7-13 are properly rejected under 35 U.S.C. §103(a) as obvious over Co, *et al.* (U.S. 2002/0176855 A1) in view of deBoer, *et al.* (U.S. Patent No. 5,747,034), Cottens, *et al.* (WO 95/16691), and Strom, *et al.* (Therapeutic Immunology, Austen *et al.*, (Ed.) Blackwell Science, Cambridge, MA 1996).

VII. ARGUMENTS

1. Rejection of Claims , 2, 4, 5, and 7-12 Under 35 U.S.C. §103(a)

The Examiner rejects claims 1, 4, 5, and 7-13 under 35 U.S.C. §103(a) as obvious over Co, *et al.* (U.S. 2002/0176855 A1) (Appendix B) in view of deBoer, *et al.* (U.S. Patent No. 5,747,034) (Appendix C), Cottens, *et al.* (WO 95/16691) (Appendix D), and Strom, *et al.* (Therapeutic Immunology, Austen *et al.*, (Ed.) Blackwell Science, Cambridge, MA 1996). (Appendix E).

It is the Examiner's position that:

> [t]he primary and secondary references provide clear teachings of combining immunosuppressives in therapeutic regimens to inhibit the immune response including antibodies and [R]apamycin . . . . . Therefore, the prior art provides motivation and expectation of success in combining immunosuppressives in therapeutic regimens including the expected advantage of additive-synergistic effects and reducing toxicity of certain immunosuppressives.

The Examiner also states that:

> Given the teachings of the prior art to combine anti-B7-1 and anti-B7 antibodies alone or in combination with other immunosuppressive therapy to inhibit immune responses, including therapeutic regimens of treating SLE alone in conjunction with the know[n] use of [R]apamycin to treat SLE alone or in combination with other immunosuppressive antibodies, including anti-B7 antibodies; one of ordinary skill in the art at the time the invention was made would have been motivated to combine anti-B7-1 and anti-B7-2 antibodies with [R]apamycin to inhibit immune responses in various therapeutic regiments including the treatment of SLE at the time the invention was made. The various dosing regiments encompasse[d] by the instant claims were obvious at the time the invention was made, given that it was well known and practice[d] at the time the invention was made to provide immunosuppressive therapy based upon the condition and needs of the patient, as evidenced by the teachings of the prior art.

For the reasons set forth below, it is Appellants' position that in view of the teachings in the cited art, and the general knowledge of the art at the time of filing, one of ordinary skill in the art would not have been motivated to combine the teachings of the cited art to produce the claimed invention. A case of *prima facie* obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. Appellants contend that the Examiner has failed to present a *prima facie* case of obviousness as there is nothing in any of the cited prior art references, or in the knowledge of the art generally, that would suggest to one of skill in the art to combine the references to arrive at the claimed invention. Moreover, even if the references are combined, there is no teaching or suggestion in the references to downmodulate an immune response, *e.g.,* an autoimmune response, by contacting immune cells from a subject with a Rapamycin compound ***and*** at

least two antibodies that bind to different B7 molecules, and certainly no expectation of success in doing so.

The present invention teaches methods of downmodulating an immune response with a combination of an anti-B7-1 antibody, an anti-B7-2 antibody ***and*** Rapamycin. In contrast, Co, *et al.* (Appendix B, originally submitted with the Office Action dated January 24, 2003) teach that immune-related or autoimmune diseases and disorders can be treated using an antibody specific to B7-2, and that treatment of these diseases may be facilitated by co-administration of an anti-B7-2 antibody with an anti-B7-1 antibody, or antibodies to the corresponding receptors, CD28 and CTLA-4. Co, *et al.* further teach that methods of treatment also involve co-administration of a humanized anti-B7-2 antibody ***or*** a humanized anti-B7-1 antibody with other standard therapy drugs (see page 10, column 2).

> Treatment of these diseases may be facilitated with coadministration of an anti-B7-2 antibody, including chimeric and humanized versions thereof, with an anti-B7-1 antibody or antibodies to the corresponding receptors, CD28 and CTLA-4.

Therefore, Co, *et al.* do not teach or suggest methods of treating any immune disease or disorder with a combination of an anti-B7-1 antibody, an anti-B7-2 antibody ***and*** Rapamycin as presently claimed. In fact, nothing in the teachings of Co, *et al.* suggests that co-administration of two antibodies that bind two different B7 molecules would be advantageous, let alone the combination of those two antibodies and Rapamycin, as claimed. Moreover, Co *et al.* do not teach, or even suggest, the administration of Rapamycin. Indeed, the very absence of Rapamycin in the list of "standard therapy drug" examples provided by Co, *et al.* clearly implies that, as experts in the field, they did not consider using Rapamycin in combination with one B7 antibody, let alone two B7 antibodies, as presently claimed.

deBoer, *et al.* (Appendix C, originally submitted with the Office Action dated January 24, 2003) disclose that the combination of anti-B7-1 antibodies and cyclosporine results in tolerance, a surprising discovery since it was previously suggested that cyclosporine ***inhibits*** anergy induction (column 5, eighth paragraph). deBoer, *et al.* teach that co-administration of a B7-1 antibody with cyclosporine A "completely blocks" T cell activation (column 25, second paragraph) and successfully inhibits T cell proliferation ***in the absence of blocking agents for B7-2*** (*e.g.*, see column 28, lines 22-28). deBoer, *et al.* further state that

> [g]iven that both B7-1 and B7-2 may provide the co-stimulatory signal to T cells for the production of IL-2 (a molecule that inactivates anergy genes), ***it is surprising that blocking only B7-1 in combination with cyclosporine results in T cell tolerance***. This may be explained by the fact that signal transduction after cross-linking with CD28 results in two independent signaling pathways, one being Cyclosporine-sensitive and one being Cyclosporine-insensitive. It may be that ***signal transduction after interaction of CD28 with B7-2 is mediated by the Cyclosporine-sensitive pathway***. (column 6, lines 27-33). (emphasis added).

Thus, Applicants respectfully submit that one of ordinary skill in the art would conclude from the teachings of deBoer, *et al.* that the administration of anti-B7-2 antibodies is unnecessary when cyclosporine is administered in combination with anti-B7-1 antibodies, *i.e.*, the combination of anti-B7-1 antibodies and cyclosporine would be equivalent to the combination of anti-B7-1 and anti-B7-2 antibodies because cyclosporine acts as a ***substitute*** for anti-B7-2 antibodies. deBoer, *et al.* therefore actually teaches away from the claimed methods. In addition, while deBoer, *et al.* suggest that other immunosuppressive agents, including Rapamycin, might be used in combination with B7-1 antibodies, they fail to provide any teaching whatsoever that any of these other immunosuppressive agents would be as effective as cyclosporine, let alone suggest the co-administration of Rapamycin with two anti-B7 antibodies, as presently claimed.

Accordingly, there is, therefore, no motivation to combine the teachings of Co, *et al.* and deBoer, *et al.* to arrive at the claimed methods. Moreover, even if the teachings of Co, *et al.* and deBoer, *et al.* are combined, they merely teach that immune disorders can be treated by inhibiting the B7 pathway using one of the following combinations (1) anti-B7-1 and anti-B7-2 antibodies (not Rapamycin); (2) anti-B7-2 antibodies and standard therapy drugs; or (3) anti-B7-1 and cyclosporine (as a substitute for anti-B7-2). Indeed, one of ordinary skill in the art, when presented with the combined teachings of deBoer, *et al.* and/or Co, *et al.* in their entirety would not have been motivated to use a combination of anti-B7-1 antibodies, anti-B7-2 antibodies and Rapamycin to treat an immune disorder, let alone be able to predict that this combination would result in improved results as demonstrated by Appellants (*e.g.*, an increased level of survival in a clinically relevant animal model when compared to the level of survival in animals treated with only B7-1 and B7-2 antibodies (see Example 2, page 49, lines 1-9, Example 3, page 49, lines 11-22, and Figure 4)).

The teachings of Cottens, *et al.* (Appendix D, originally submitted with the Office Action dated January 24, 2003) and Strom, *et al.* (Appendix E, originally submitted with the Office Action dated January 24, 2003), either alone or in combination, do not cure the deficiencies of Co, *et al.* and deBoer, *et al.* Cottons, *et al.* merely teach novel Rapamycin derivatives that have "an improved pharmacological profile over Rapamycin, exhibit greater stability and bioavailability, allow for greater ease in producing formulations, and are more potent immunosuppressants" (page 2, second paragraph). Cottens, *et al.* generally suggest that the novel compounds might be used in combination with other immunosuppressive drugs or immunosuppressive monoclonal antibodies, but provide no specific teaching of any combination that is effective in inducing anergy. Strom, *et al.* merely teach a multi-tiered approach to immunosuppressive therapy. Strom, *et al.* further disclose that the majority of basic protocols involve a combination of cyclosporine or FK506 plus corticosteroids with or without azathioprine, and suggest that anti-lymphocyte globulin or OKT3 might also added to reduce the dose of cyclosporine required (page 454). Thus, Strom, *et al.* merely include Rapamycin in their general list of immunosuppressants with nothing more.

In short, none of the cited references alone or in combination suggest the use of a combination of Rapamycin with at least two B7 antibodies as presently claimed. At best, the cited references might be viewed as generally providing the suggestion to try various combinations of immunosuppressive antibodies and immunosuppressive agents. Indeed, Appellants respectfully submit that the Examiner has failed to point to any teaching in the Co, *et al.*, deBoer, *et al.* and/or Cottens, *et al.* and Strom, *et al.* references that would compel one of ordinary skill in the art to make the claimed invention. As the Board is well aware, the prior art must suggest "to those of ordinary skill in the art that they ***should*** make the claimed composition or device, or carry out the claimed process" and [b]oth the suggestion and the reasonable expectation of success ***must be founded in the prior art, not in the applicant's disclosure*** (emphasis added)." *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988) (Appendix F).

Appellants further rely on to *Arkie Lures v. Larew Tackle*, 119 F.3d 953, 43 U.S.P.Q. 2d 1294 (Fed. Cir. 1997) (Appendix G) to support their position. In *Arkie Lures*, the Larew invention was directed to a "salt-impregnated fishing lure." In that

case, the CAFC overturned the district court's finding of obviousness. The CAFC agreed that "[t]he use of salty bait to catch fish was known, [and] plastisol lures were known." *Id* at page 956. However, the CAFC found that although the literature on "fishing lures is apparently quite extensive, but despite the long use of salty lures and plastic lures, no reference was cited that showed or suggested this combination." *Id* at page 956. The CAFC continued and stated that "[t]he evidence showed the complexity of the plastic fishing lure art. Those in the field of the invention viewed Larew's invention not as a simple concept of adding salty taste to a known lure, but as a complex combination requiring experience of fishing and fishing lures and the technology of plastics." *Id* at page 957. The court further stated that:

> No prior art showed or suggested the combination of a plastisol lure with salt, although the prior art was extensive as to the separate elements, and suggested including organic attractants in plastic lures. . . . The question is not whether salt "could be used," as the district court concluded, but whether it was obvious to do so in light of all the relevant factors. . . .***It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements.*** Indeed, the years of use of salty bait and of plastic lures, without combining their properties, weighs on the side of unobviousness of the combination (emphasis added).

Id at pages 957 and 958.

Similar to the situation in the *Arkie Lures* case, even if the prior art contained the separate elements of the presently claimed methods, these individual teachings are insufficient to establish the obviousness of the claimed invention absent some teaching or suggestion in the art to combine and modify the teachings of those references to arrive at the claimed invention.

In further support of their position, Appellants point to the CAFC decision in *In re Rouffet*, (149 F.3d 1350) (Fed. Cir. 1998) (Appendix H). Rouffet filed a patent application directed to technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites. Rouffet taught changing the shape of the beam transmitted by the satellite's antenna to a fan-shaped beam. The

Examiner rejected Rouffet's claims as unpatentable over U.S. Patent number 5,199,672 (King) in view of U.S. Patent number 4,872,015 (Rosen) and a report titled "A Novel Non-Geostationary Satellite Communications System" (Ruddy). The CAFC found that:

> [although] the board did not err in finding that the combination of King, Rosen, and Ruddy contains all of the elements claimed in Rouffet's application. . .the Board reversibly erred in determining that one of skill in the art would have been motivated to combine these references in a manner that rendered the claimed invention obvious. Indeed, ***the Board did not identify any motivation to choose these references for combination.*** (emphasis added).

Id at page 1357.

Similarly, it is Appellants' position that the Examiner has failed to point to ***any motivation*** to combine the cited prior art references, let alone combine them in performing the claimed method. In *Rouffet* the CAFC continued:

> [b]ecause the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. See In re Gorman, 933 F.2d 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed Cir. 1991). ***Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness.*** This court reverses the rejection over the combination of King, Rosen, and Ruddy.

In at page 1357.

Additional support for Appellants' position that the claimed invention is not obvious is found in *In re Vaeck* (*In re Vaeck* 947 F.2d 488. (Fed. Cir. 1991)) (Appendix I). In *Vaeck* the invention was drawn to "a chimeric (*i.e.*, hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing the Bacillus gene in a host cyanobacterium, so as to produce the desired insecticidal protein (footnote omitted)." *Id* at page 490. The prior art was applied in various combinations

against the claims. The primary reference (Dzelzkalns) taught the expression of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT) in cyanobacteria. The secondary references taught, *inter alia,* "expression of genes encoding certain *Bacillus* insecticidal proteins" in other host cells; "the initiation specificities *in vitro* of DNA-dependent RNA polymerases purified from two different species of cyanobacteria (footnote omitted);" and "host-vector systems for gene cloning in the cyanobacterium." *Id* at page 491. The Examiner's position was that:

> it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes [which had been expressed in heterologous hosts in the teachings of the prior art] for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The Examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes.

Id at page 492. The CAFC disagreed with the PTO's position and found that the teachings of the prior art cited were not sufficient to support the interchangeability of bacteria and cyanobacteria as host organisms for the expression of heterologous insecticidal proteins. The CAFC stated that "there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria." *Id* at page 493. The court further stated that while the prior art disclosed "expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere do these references disclose or suggest expression of such genes in transformed cyanobacterial hosts. . . . [w]hile it is true that bacteria and cyanobacteria are now both classified as prokaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends." *Id* at pages 493 and 494.

The CAFC contrasted its findings in *In re Vaeck* with those in *In re O'Farrell* stating "[i]n contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art." *Id* at page 495. In *O'Farrell* the invention was directed to a "method for producing a predetermined protein in a stable form in a transformed host species of bacteria." *In re O'Farrell* 853 F.2d 894. 1988. 7 U.S.P.Q. 2d (BNA) 1673 (Appendix J). The prior art (Polisky) taught a previous attempt to "control the expression of cloned heterologous genes inserted into bacteria." *Id* at page 899. The prior art differed from the claim at issue, however, because it taught a method of expressing "a segment of DNA from a frog that coded for ribosomal RNA," which is normally not translated into protein. Although ribosomal RNA is not normally translated into protein, the court found that in the prior art publication by Polisky the authors were "obviously interested in using their approach to make heterologous proteins in bacteria." *Id* at page 900. The CAFC referred to the Polisky paper which stated:

> In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of Xenopus [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

Id at page 900 (quoting from Polisky *et al.* at page 4904). The court stated that "[t]he authors of the Polisky paper ***explicitly pointed out*** that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a 'fused protein' consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain." (emphasis added) *Id* at page 901. The court also referred to a passage in the Polisky reference, wherein the authors stated that "[i]f an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a read-through transcript might allow for extensive translation of a functional eukaryotic polypeptide." *Id* at page 901 (quoting from Polisky *et al.*). The CAFC upheld the PTO decision that the claims in *O'Farrell* were obvious over Polisky because:

> virtually everything in the claims was present in the prior art. . . . The main difference is that in Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. . . .Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, 'a read-through transcript might allow for extensive translation of a functional eukaryotic polypeptide.' ***Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins***. (emphasis added)

Id at 901.

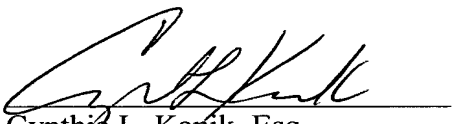
It is Appellants' position that, as in *In re Vaeck*, there is no teaching, either explicit or implicit, in any of the references cited by the Examiner, which would have impelled one of ordinary skill in the art to make the instantly claimed invention and at most, the teachings of the cited references merely provide the motivation to test any and all combinations of immunosuppressive antibodies and immunosuppressive agents.

Appellants submit that the Examiner has used Appellants' invention as a blueprint to combine the aforementioned references. As the Board is well aware, the use of hindsight in the selection of references is forbidden. (See *In re Gorman*, 933 F.2d 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed. Cir. 1991)) (Appendix K). Appellants respectfully submit that the art cited by the Examiner is directed to individual elements of Appellants' invention, and there is no teaching in the references or the known art at the time of filing that would motivate one skilled in the art to combine the references. The Examiner has, therefore, improperly relied on hindsight obtained from Appellants' own invention to combine the cited references.

Moreover, even if the Board finds that the motivation existed to combine the teachings of the cited references, Appellants submit that the combined teachings of the references do not teach each and every element of the claimed methods. In particular, none of the references, either alone or in combination, teach methods of downmodulating an immune response utilizing a ***Rapamycin compound*** in combination with ***at least two antibodies*** that bind to ***different B7 molecules***.

In summary, Appellants contend that the Examiner has improperly relied on hindsight reconstruction obtained from Appellants' invention in combining the cited references, and as such, has failed to provide a *prima facie* case of obviousness. Moreover, Appellants submit that even if combined, the cited references do not teach, suggest or enable the claimed methods presently on appeal. Appellants therefore request that the Board withdraw the Examiner's rejection of the claims under 35 U.S.C. §103(a).

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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Dated: April 15, 2005

CLAIMS APPENDIX

APPENDIX A

1. (Previously Presented) A method for downmodulating an immune response comprising contacting immune cells from a subject with a Rapamycin compound in combination with at least two antibodies, wherein each of said antibodies binds to a different B7 molecule selected from the group consisting of B7-1, B7-2, B7-H1, or B7RP-1.

2. (Canceled)

3. (Canceled)

4. (Previously Presented) The method of claim 1, wherein the step of contacting is performed *in vivo*.

5. (Previously Presented) A method for downmodulating an immune response in a subject having an autoimmune disorder comprising contacting immune cells from the subject with a Rapamycin compound in combination with at least two antibodies, wherein each of said antibodies binds to a different B7 molecule selected from the group consisting of B7-1, B7-2, B7-H1, or B7RP-1.

6. (Canceled)

7. (Previously Presented) The method of claim 5, wherein the autoimmune disorder is systemic lupus erythematosis.

8. (Previously Presented) A method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis comprising administering to the subject an antibody that binds to B7-1, an antibody that binds to B7-2, and a Rapamycin compound, wherein the antibody that binds to B7-1 and the antibody that binds to B7-2 are administered over at least one short course of therapy.

9. (Previously Presented) A method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis comprising administering to the subject an antibody that binds to B7-1, an antibody that binds to B7-2, and a Rapamycin compound, wherein the Rapamycin compound is administered over at least one intermediate course of therapy.

10. (Previously Presented) A method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis comprising administering to said subject an antibody that binds B7-1, an antibody that binds B7-2, and a Rapamycin compound, wherein said Rapamycin compound is administered over at least one extended course of therapy.

11. (Previously Presented) A method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis comprising administering to said subject an antibody that binds B7-1, an antibody that binds B7-2, and a Rapamycin compound, wherein said Rapamycin compound is administered according to an early dosing regimen.

12. (Previously Presented) A method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis comprising administering to said subject an antibody that binds B7-1, an antibody that binds B7-2, and a Rapamycin compound, wherein said Rapamycin compound is administered according to a late dosing regimen.

13. (Previously Presented) A method for downmodulating an immune response in a subject suffering from systemic lupus erythematosis comprising administering to said subject an antibody that binds B7-1, an antibody that binds B7-2, a Rapamycin compound, and an immunosuppressing agent, wherein said immunosuppressing agent is selected from the group consisting of FK506, Cyclosporine A and cyclophosphamide.

EVIDENCE APPENDIX

APPENDIX L

Appendix B is a copy of U.S. 2002/0176855 A1 (Co, *et al.*), originally submitted with the Office Action mailed from the U.S. Patent and trademark Office on January 24, 2003.

Appendix C is a copy of U.S. Patent No. 5,747,034 (deBoer, *et al.*), originally submitted with the Office Action mailed from the U.S. Patent and trademark Office on January 24, 2003.

Appendix D is a copy of WO 95/16691 (Cottens, *et al.*), originally submitted with the Office Action mailed from the U.S. Patent and trademark Office on January 24, 2003.

Appendix E is a copy of Strom, *et al.* (Therapeutic Immunology, Austen *et al.*, (Ed.) Blackwell Science, Cambridge, MA 1996), originally submitted with the Office Action mailed from the U.S. Patent and trademark Office on January 24, 2003.

Appendix F is a copy of *In re Dow Chemical Co.* 837 F.2d 469 (Fed. Cir. 1988), first cited in the present Brief.

Appendix G is a copy of *Arkie Lures v. Larew Tackle*, 119 F.3d 953 (Fed. Cir. 1997), first cited in the present Brief.

Appendix H is a copy of *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998), first cited in the present Brief.

Appendix I is a copy of *In re Vaeck* 947 F.2d 488 (Fed. Cir. 1991), first cited in the present Brief.

Appendix J is a copy of *In re O'Farrell* 853 F.2d 894 (Fed. Cir. 1988), first cited in the present Brief.

Appendix K is a copy of *In re Gorman*, 933 F.2d 982 (Fed. Cir. 1991), first cited in the present Brief.

RELATED PROCEEDINGS APPENDIX

APPENDIX M

As indicated in Section II of this Appeal Brief, no other appeals or interferences are known to Appellants, Appellants' legal representative, or the assignees.

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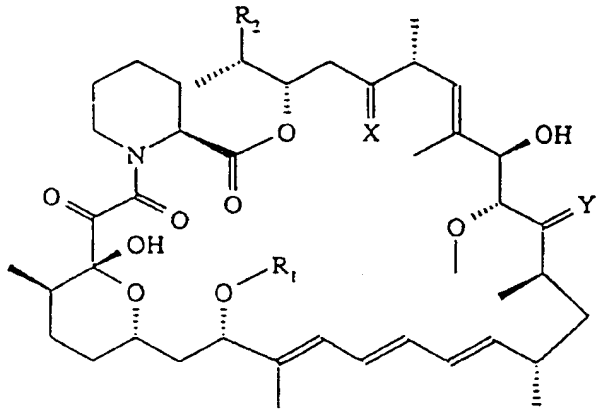
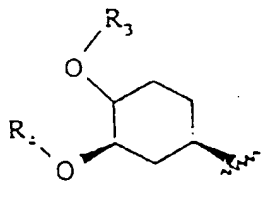
(54) Title: RAPAMYCIN DERIVATIVES USEFUL AS IMMUNOSUPPRESSANTS

(57) Abstract

Novel demethoxy derivatives of rapamycin of formula (I) are found to have pharmaceutical utility, particularly as an immunosuppressants. In formula (I) R_2 = formula (II) or formula (III), X, Y, R_1, R_3, R_3, R_4, R_5 are as defined in the application.



(I)



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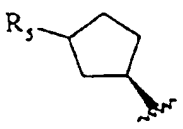

(III)

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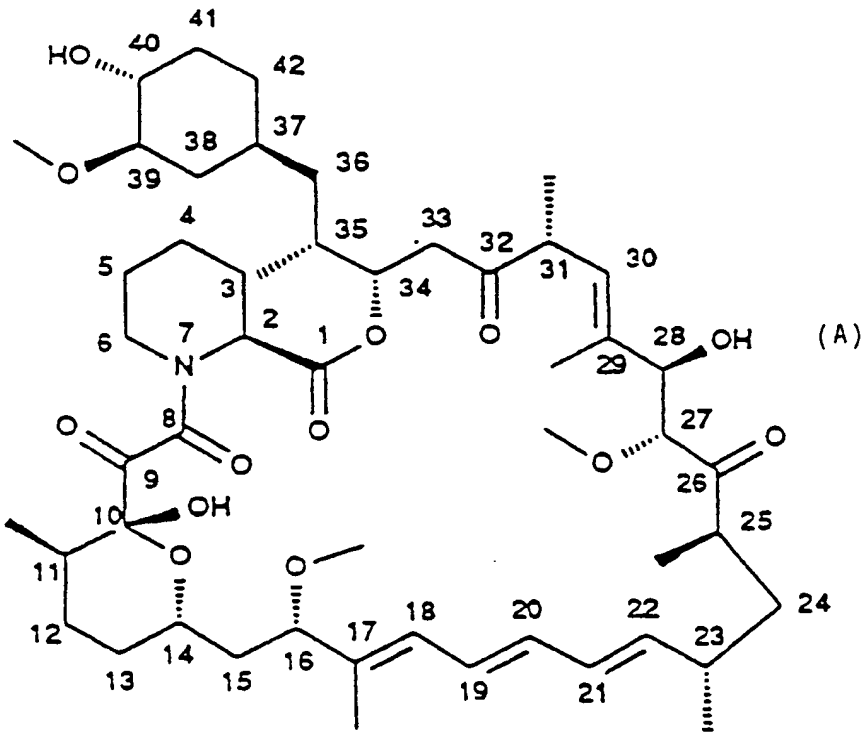
RAPAMYCIN DERIVATIVES USEFUL AS IMMUNOSUPPRESSANTS.

This invention comprises novel demethoxy derivatives of rapamycin, such derivatives having pharmaceutical utility, especially as immunosuppressants.

Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus, having the structure depicted in Formula A:



See, e.g., McAlpine, J.B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S.L., et al., J. Am. Chem. Soc. (1991) 113: 7433; US Patent No. 3 929 992. (There have been various numbering schemes proposed for rapamycin. To avoid confusion, when specific

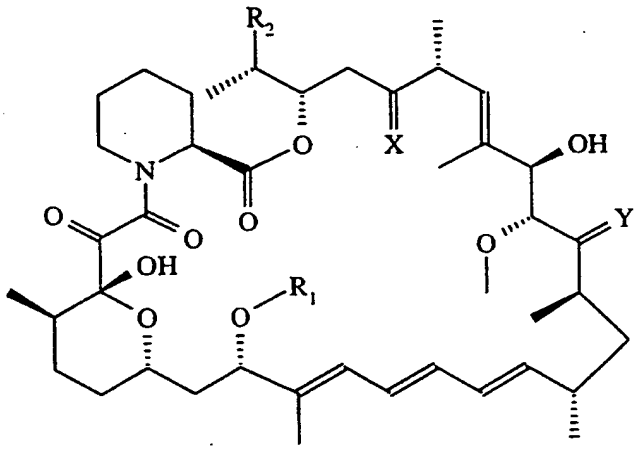
rapamycin derivatives are named herein, the names are given with reference to rapamycin using the numbering scheme of formula A.) Rapamycin is an extremely potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability as well as its high toxicity. Moreover, rapamycin is highly insoluble, making it difficult to formulate stable galenic compositions. Numerous derivatives of rapamycin are known. Certain 16-O-substituted rapamycins are disclosed in WO 94/02136, the contents of which are incorporated herein by reference. 40-O-substituted rapamycins are described in, e.g., in US 5 258 389 and PCT/EP 93/02604 (O-aryl and O-alkyl rapamycins); WO 92/05179 (carboxylic acid esters), US 5 118 677 (amide esters), US 5 118 678 (carbamates), US 5 100 883 (fluorinated esters), US 5 151 413 (acetals), and US 5 120 842 (silyl ethers), all of which are incorporated herein by reference. 32-O-dihydro or substituted rapamycin are described, e.g., in US 5 256 790, incorporated herein by reference.

It has now surprisingly been discovered that certain novel demethoxy derivatives of rapamycin (the Novel Compounds) have an improved pharmacological profile over rapamycin, exhibit greater stability and bioavailability, allow for greater ease in producing galenic formulations, and are more potent immunosuppressants. The Novel Compounds comprise rapamycins wherein the methoxy group(s) at position 16 and/or position 39 of rapamycin is deleted and replaced with a selected substituent. Without intending to be bound to any particular theory, we have hypothesized that these particular methoxy groups on rapamycin are targets for metabolic attack and can be replaced with particular selected substituents, optionally in combination with certain further modifications to the molecule, so that activity is retained, or even in some cases, enhanced, and at the same time, susceptibility to metabolic attack is reduced.

The Novel Compounds particularly include rapamycins (i) wherein the methoxy group at the 16 position is replaced with another substituent, preferably (optionally hydroxy-substituted) alkynyloxy, and/or (ii) wherein the methoxy group at the 39 position is deleted together with the 39 carbon so that the cyclohexyl ring of rapamycin

becomes a cyclopentyl ring lacking the 39 position methoxy group (i.e., 39-demethoxy-40-desoxy-39-substituted-42-nor-rapamycins, sometimes referred to herein simply as cyclopentyl rapamycins). The remainder of the molecule is as for rapamycin or its immunosuppressive derivatives and analogues, e.g., as described above. Optionally, the molecule is further modified, e.g., such that the hydroxy at the 40-position of rapamycin is alkylated, and/or the 32-carbonyl is reduced.

Preferably, the Novel Compounds are those having the structure of Formula I:



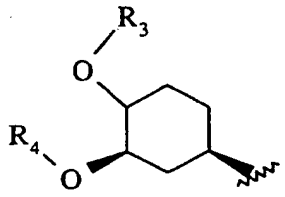
Formula I

wherein

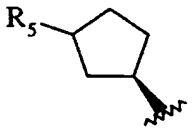
R_1 is selected from alkyl, alkenyl, alkynyl, hydroxyalkenyl, hydroxyalkyl, hydroxyalkynyl, aryl, thioalkyl, arylalkyl, hydroxyarylalkyl, hydroxyaryl, dihydroxyalkyl, hydroxyalkoxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, alkoxyarylalkyl, haloalkyl, haloaryl, haloarylalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylamidoalkyl, acylamidoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and alkylsilyl; preferably an unsaturated substituent; more preferably an aromatic or alkynyl substituent; more

preferably alkynyl, hydroxyalkynyl, benzyl, alkoxybenzyl, or chlorobenzyl (wherein the substituted benzyl is *ortho*-substituted); most preferably alkynyl or hydroxyalkynyl;

R_2 is selected from formula II or formula III:



Formula II



Formula III

wherein

R_3 is selected from H, alkyl, alkenyl, alkynyl, aryl, thioalkyl, arylalkyl, hydroxyarylalkyl, hydroxyaryl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkoxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylamidoalkyl, acylamidoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and alkylsilyl; preferably hydroxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, alkoxyalkyl, and aminoalkyl; especially hydroxyethyl, hydroxypropyl, hydroxyethoxyethyl, methoxyethyl and acetylaminoethyl;

R_4 is H, methyl or together with R_3 forms C_{2-6} alkylene;

R_5 is substituted or unsubstituted acyl (e.g., formyl, carboxy, amide or ester), oxymethyl, iminomethyl, or dioxymethylyne (e.g., -O-CH-O-); preferably (i) oxymethyl, for example, hydroxymethyl, e.g., generally R_6O-CH_2-, wherein R_6 is selected from H, alkyl, alkenyl, alkynyl, aryl, amino, acyl (e.g., alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, hydroxyalkylcarbonyl, aminoalkylcarbonyl, or formyl), thioalkyl, arylalkyl, hydroxyarylalkyl, hydroxyaryl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkoxyalkyl,

hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylamidoalkyl, acylamidoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and alkylsilyl; (ii) acyl, for example, (4-methyl-piperazin-1-yl)-carbonyl, (morpholin-4-yl)-carbonyl, or N-methyl-N-(2-pyridin-2-yl-ethyl)-carbamoyl, e.g., generally R_7CO-, wherein R_7 is selected from H, alkyl, hydroxy, alkoxy, aryloxy, amido, alkamido, a residue of an amino acid, or N,N-disubstituted-amido wherein the substituents (a) are selected from alkyl, aryl, arylalkyl or alkylaryl or (b) form a heterocyclic structure (e.g., morpholino or piperazino); (iii) iminomethyl, for example, p-toluenesulfonylhydrazonomethyl, e.g., generally R_8NCH-, wherein R_8 is alkyl, aryl, amino, alkylamino, arylamino, or arylsulfonylamino; or (iv) dioxysubstituted dioxymethylyne compounds, e.g., O,O-(alkylene)-dioxymethylyne (i.e., wherein the two oxygens are linked by an alkylene group); and
X and Y are independently selected from O, (H, OH), and (H, OR_9) wherein R_9 is selected from alkyl (preferably C_{1-4} alkyl), acyl (e.g., alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, hydroxyalkylcarbonyl, aminoalkylcarbonyl, or formyl), or aryl ;

wherein "alk" or "alkyl" refers to a C_{1-10} (preferably C_{1-6}) aliphatic substituent (branched, linear, or cyclic), optionally interrupted by an oxy (-O-) linkage; and "ar" or "aryl" refers to a monocyclic, optionally heterocyclic, optionally substituted, C_{4-14} aromatic substituent (e.g., tolyl, phenyl, benzyl, pyridyl, and the like);
provided that when R_2 is of formula II, then R_1 is other than methyl and (i) R_3 is selected from hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, and aminoalkyl; and/or (ii) X is other than O; and/or (iii) R_1 is (optionally hydroxy-substituted) alkynyl , preferably (optionally hydroxy-substituted) alk-2-ynyl, e.g. prop-2-ynyl, but-2-ynyl, pent-2-ynyl, or 4-hydroxy-but-2-ynyl;
and further provided that when R_1 is methyl, R_2 is of Formula III.

Demethoxy rapamycins of Formula I also include

(a) the 16-O substituted rapamycins wherein R_1 is selected from (i) benzyl, *ortho*-alkoxybenzyl, and chlorobenzyl (especially benzyl or *ortho*-methoxybenzyl), or (ii) (optionally hydroxy-substituted) alkynyl , preferably (optionally hydroxy-substituted) alk-

2-ynyl, especially (i) prop-2-ynyl, but-2-ynyl, pent-2-ynyl, and 4-hydroxy-but-2-ynyl; R_2 is of formula II; R_3 is selected from H, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, and aminoalkyl; R_4 is methyl; and X and Y are independently selected from O, (H,OH), and (H, C_{1-4}alkoxy);

and most preferably, the 16-O substituted rapamycins wherein R_1 is alkynyl or hydroxyalkynyl, especially (optionally hydroxy substituted) C_{3-6} alk-2-ynyl; R_2 is of formula II; R_3 is selected from H, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl; R_4 is methyl; and X and Y are O;

(b) the 16-O-substituted rapamycins wherein R_1 is selected from alkyl, alkyenyl, alkynyl, aryl, thioalkyl, arylalkyl, hydroxyarylalkyl, hydroxyaryl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkoxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylamidoalkyl, acylamidoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and alkylsilyl (especially alkynyl), wherein "alk" refers to C_{1-10} aliphatic substituent (branched, linear, or cyclic), optionally interrupted by an oxy (-O-) linkage, and aryl refers to a monocyclic aromatic substituent; provided that where R_1 is methyl, the compound is 16-epi-rapamycin; R_2 is of formula II; R_3 is H; R_4 is methyl; and X and Y are O; and

(c) the cyclopentyl rapamycins wherein R_2 is of Formula III, and R_1, R_5, X, and Y are as defined above; e.g., where R_1 is methyl, X and Y are O, and R_5 is substituted or unsubstituted acyl (e.g., formyl, carboxy, amide or ester), oxymethyl, iminomethyl, or dioxymethylyne (e.g., -O-CH-O-); e.g., (i) oxymethyl, e.g., R_6O-CH_2-, wherein R_6 is selected from H, alkyl, alkyenyl, alkynyl, aryl, thioalkyl, arylalkyl, hydroxyarylalkyl, hydroxyaryl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkoxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylamidoalkyl, acylamidoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and alkylsilyl; (ii) acyl, e.g., R_7CO-, wherein R_7 is selected from H, alkyl, hydroxy, alkoxy, aryloxy, amido, alkamido, a residue of an amino acid, or N,N-substituted-amido wherein the substituent forms a heterocyclic structure (e.g., morpholino or piperazino); (iii) iminomethyl, e.g., alkyliminomethyl, aryliminomethyl, or hydrazonomethyl; or (iv) dioxysubstituted

dioxymethylyne compounds, e.g., O,O-(alkylene)-dioxymethylyne (i.e., wherein the two oxygens are linked by an alkylene group); wherein "alk-" refers to a C_{1-6} aliphatic group (linear, branched, or cyclic) preferably C_{1-3}, in which the carbon chain may be optionally interrupted by an ether (-O-) linkage; and aryl refers to an aromatic group, preferably a monocyclic aromatic group.

Especially preferred compounds of Formula I include

1. 16-demethoxy-16-(pent-2-ynyl)oxy-rapamycin
2. 16-demethoxy-16-(but-2-ynyl)oxy-rapamycin
3. 16-demethoxy-16-(propargyl)oxy-rapamycin
4. 16-demethoxy-16-(4-hydroxy-but-2-ynyl)oxy-rapamycin
5. 16-demethoxy-16-benzyloxy-40-O-(2-hydroxyethyl)-rapamycin
6. 16-demethoxy-16-benzyloxy-rapamycin
7. 16-demethoxy-16-*ortho*-methoxybenzyl-rapamycin
8. 16-demethoxy-40-O-(2-methoxyethyl)-16-(pent-2-ynyl)oxy-rapamycin
9. 39-demethoxy-40-desoxy-39-formyl-42-nor-rapamycin
10. 39-demethoxy-40-desoxy-39-hydroxymethyl-42-nor-rapamycin
11. 39-demethoxy-40-desoxy-39-carboxy-42-nor-rapamycin
12. 39-demethoxy-40-desoxy-39-(4-methyl-piperazin-1-yl)carbonyl-42-nor-rapamycin
13. 39-demethoxy-40-desoxy-39-(morpholin-4-yl)carbonyl-42-nor-rapamycin
14. 39-demethoxy-40-desoxy-39-[N-methyl, N-(2-pyridin-2-yl-ethyl)]carbamoyl-42-nor-rapamycin
15. 39-demethoxy-40-desoxy-39-(p-toluenesulfonylhydrazonomethyl)-42-nor-rapamycin

The compounds are produced from rapamycin or a rapamycin derivative generally as follows:

1. When the compound desired is of Formula I wherein R_1 is other than methyl, the modification at the 16-O can be produced either (i) by reaction of rapamycin or a rapamycin derivative with SeO_2 and a compound R_1-OH under suitable reaction conditions, e.g., at elevated temperatures, wherein R_1 is as defined above; or preferably (ii) by reaction of rapamycin or a rapamycin derivative with an acid, e.g., p-

toluenesulphonic acid, and a nucleophile, e.g., R_1-OH, at room temperature, in a suitable aprotic solvent, e.g., dichloromethane, acetonitrile, or THF.

2. When the compound desired is of formula I where R_2 is of formula II and R_3 is other than H, for example, O-alkylation at the C40 hydroxy is accomplished by reaction with an organic radical attached to a leaving group (e.g., R_3-Z where R_3 is an organic radical as defined above, e.g., an alkyl, allyl, or benzyl moiety, which is desired as the O-substituent, and Z is the leaving group, e.g., $CCl_3C(NH)O$ or CF_3SO_3) under suitable reaction conditions, e.g., in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when Z is $CCl_3C(NH)O$ or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when Z is CF_3SO_3, or analogously to the methods described in US 5 258 389 or PCT/EP 93/02604 for 40-O alkylation of rapamycin.

3. When the compound desired is of formula I where R_2 is of formula III, conversion of the cyclohexyl ring of formula II to the cyclopentyl ring of formula III is accomplished by reaction with morpholinosulphur trifloride to obtain the aldehyde compound (e.g., where R_5 is formyl). This compound thus obtained may then be oxidized from the aldehyde to the carboxylic acid (e.g., where R_5 is carboxy), or reduced from the aldehyde to the alcohol (e.g., where R_5 is hydroxymethyl). Further O-substitution or modification to make the other compounds of the invention is performed according to processes known to those skilled in the art, e.g., the following general processes: (i) for oxymethyl derivatives, the alcohol compound is reacted analogously as described above for 40-O-substitution; (ii) for acyl derivatives, the carboxylic acid compound is reacted with the desired amine or alcohol in the presence of an activating or coupling reagent, e.g., oxalylchloride or dicyclohexylcarbodiimide, to give the desired amide or ester compounds respectively; and (iii) for iminomethyl or dioxymethylyne compounds, the aldehyde compound is condensed with the desired amine or alkylenediol, respectively, under acidic conditions.

4. When the compound desired is of formula I where X is other than O, the 32-O-dihydro compound (where X is (H,OH)) is prepared by O-protecting the hydroxy groups, e.g., at positions 28 and 40 of rapamycin, e.g., using triethylsilyl ether protecting

groups, reducing the protected compound, e.g., using L-selectride, and optionally deprotecting, e.g., under mildly acidic conditions, analogously to the method described in US 5 256 790 for preparation of 32-O-dihydro-rapamycin from rapamycin. Where substitution at the 32 hydroxy is desired, the 28,40-O,O-protected compound is alkylated, e.g., as described for 40-O alkylation above, acylated, or otherwise O-substituted, e.g., analogously to the procedures described in US 5 256 790.

The above processes may be carried out in any order, preferably using rapamycin as the ultimate starting material. Where necessary, the starting materials and intermediates may be protected (e.g., O-protected as described in process 4) before carrying out the above reaction(s) and then deprotected to obtain the desired final product.

The Novel Compounds are particularly useful for the following conditions:

a) Treatment and prevention of organ or tissue transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants; including treatment and prevention of acute rejection; treatment and prevention of hyperacute rejection, e.g., as associated with xenograft rejection; and treatment and prevention of chronic rejection, e.g., as associated with graft-vessel disease. The Novel Compounds are also indicated for the treatment and prevention of graft-versus-host disease, such as following bone marrow transplantation.

b) Treatment and prevention of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific autoimmune diseases for which the compounds of the invention may be employed include, autoimmune hematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's

disease) endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy) and juvenile dermatomyositis.

c) Treatment and prevention of asthma.

d) Treatment of multi-drug resistance (MDR). The Novel Compounds suppress P-glycoproteins (Pgp), which are the membrane transport molecules associated with MDR. MDR is particularly problematic in cancer patients and AIDS patients who will not respond to conventional chemotherapy because the medication is pumped out of the cells by Pgp. The Novel Compounds are therefore useful for enhancing the efficacy of other chemotherapeutic agents in the treatment and control of multidrug resistant conditions such as multidrug resistant cancer or multidrug resistant AIDS.

e) Treatment of proliferative disorders, e.g. tumors, hyperproliferative skin disorder and the like.

f) Treatment of fungal infections.

g) Treatment and prevention of inflammation, especially in potentiating the action of steroids.

h) Treatment and prevention of infection, especially infection by pathogens having Mip or Mip-like factors.

The invention thus provides the Novel Compounds described herein, for use as novel intermediates or as pharmaceuticals, methods of treating or preventing the above-described disorders by administering an effective amount of a Novel Compound to a patient in need thereof, use of a Novel Compound in the manufacture of a medicament for treatment or prevention of the above-described disorders, and pharmaceutical compositions comprising a Novel Compound in combination or association with a pharmaceutically acceptable diluent or carrier.

The Novel Compounds are utilized by administration of a pharmaceutically effective dose in pharmaceutically acceptable form to a subject in need of treatment. Appropriate dosages of the Novel Compounds will of course vary, e.g. depending on the condition to be treated (for example the disease type or the nature of resistance), the effect desired and the mode of administration.

In general however satisfactory results are obtained on administration orally at dosages on the order of from 0.05 to 5 or up to 10mg/kg/day, e.g. on the order of from 0.1 to 2 or up to 7.5 mg/kg/day administered once or, in divided doses 2 to 4x per day, or on administration parenterally, e.g. intravenously, for example by i.v. drip or infusion, at dosages on the order of from 0.01 to 2.5 up to 5 mg/kg/day, e.g. on the order of from 0.05 or 0.1 up to 1.0 mg/kg/day. Suitable daily dosages for patients are thus on the order of 500 mg p.o., e.g. on the order of from 5 to 100 mg p.o., or on the order of from 0.5 to 125 up to 250 mg i.v., e.g. on the order of from 2.5 to 50 mg i.v..

Alternatively and even preferably, dosaging is arranged in patient specific manner to provide pre-determined trough blood levels, e.g. as determined by RIA technique. Thus patient dosaging may be adjusted so as to achieve regular on-going trough blood levels as measured by RIA on the order of from 50 or 150 up to 500 or 1000ng/ml, i.e. analogously to methods of dosaging currently employed for Ciclosporin immunosuppressive therapy.

The Novel Compounds may be administered as the sole active ingredient or together with other drugs. For example, in immunosuppressive applications such as prevention and treatment of graft vs. host disease, transplant rejection, or autoimmune disease, the Novel Compounds may be used in combination with cyclosporins or ascomycins, or their immunosuppressive analogs, e.g., cyclosporin A, cyclosporin G, FK-506, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; brequinar; leflunomide; mizoribine; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD25, CD28, CTLA4, B7, CD45, or CD58 or their ligands; or other immunomodulatory compounds.

For immunosuppressive applications, e.g., treatment and prevention of organ or tissue transplant rejection, the combination is most preferably with IL-2 transcription inhibitors such as the immunosuppressive cyclosprins (e.g., cyclosporin A) and ascomycins (e.g., FK-506). For anti-inflammatory applications, the Novel Compounds can also be used together with anti-inflammatory agents, e.g., corticosteroids. For anti-infective applications, the Novel Compounds can be used in combination with other anti-infective agents, e.g., anti-viral drugs or antibiotics.

The Novel Compounds are administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise, e.g. from 1 to 50 mg of a compound of the invention, usually 1 to 10 mg. Pharmaceutical compositions comprising the novel compounds may be prepared analogously to pharmaceutical compositions comprising rapamycin, e.g., as described in EPA 0 041 795, which would be evident to one skilled in the art.

The pharmacological activities of the Novel Compounds are demonstrated in, e.g., the following tests:

1. Mixed lymphocyte reaction (MLR)

The Mixed Lymphocyte Reaction was originally developed in connection with allografts, to assess the tissue compatibility between potential organ donors and recipients, and is one of the best established models of immune reaction in vitro. A murine model MLR, e.g., as described by T.Meo in "Immunological Methods", L. Lefkovits and B. Peris, Eds., Academic Press, N.Y. pp. 227-239 (1979), is used to demonstrate the immunosuppressive effect of the Novel Compounds. Spleen cells (0.5×10^6) from Balb/c mice (female, 8-10 weeks) are co-incubated for 5 days with 0.5×10^6 irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8-10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb/c spleen cells which can be measured by labeled precursor incorporation into the DNA.

Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The antiproliferative effect of the Novel Compounds on the Balb/c cells is measured at various dilutions and the concentration resulting in 50% inhibition of cell proliferation (IC_{50}) is calculated. All of the exemplified Novel Compounds are active in this assay. The alkynyl derivatives of the examples are particularly potent immunosuppressants, with an IC_{50} in this assay relative to rapamycin of 0.3 - 0.8, i.e., up to 3x more active than rapamycin.

2. IL-6 mediated proliferation

The capacity of the Novel Compounds to interfere with growth factor associated signalling pathways is assessed using an interleukin-6 (IL-6)-dependent mouse hybridoma cell line. The assay is performed in 96-well microtiter plates. 5000 cells/well are cultivated in serum-free medium (as described by M. H. Schreier and R. Tees in Immunological Methods, I. Lefkovits and B. Pernis, eds., Academic Press 1981, Vol. II, pp. 263-275), supplemented with 1 ng recombinant IL-6/ml. Following a 66 hour incubation in the absence or presence of a test sample, cells are pulsed with 1 μCi (3-H)-thymidine/well for another 6 hours, harvested and counted by liquid scintillation. (3-H)-thymidine incorporation into DNA correlates with the increase in cell number and is thus a measure of cell proliferation. A dilution series of the test sample allows the calculation of the concentration resulting in 50% inhibition of cell proliferation (IC_{50}). All of the exemplified Novel Compounds are active in this assay. The alkynyl derivatives of the examples are particularly potent immunosuppressants, with an IC_{50} in this assay relative to rapamycin of from 0.2 to 0.9, i.e., up to 5x more active than rapamycin.

3. Macrophilin binding assay

Rapamycin and the structurally related immunosuppressant, FK-506, are both known to bind in vivo to macrophilin-12 (also known as FK-506 binding protein or FKBP-12), and this binding is thought to be related to the immunosuppressive activity of these compounds. The Novel Compounds also bind strongly to macrophilin-12, as is demonstrated in a competitive binding assay. In this assay, FK-506 coupled to BSA is

used to coat microtiter wells. Biotinylated recombinant human macrophilin-12 (biot-MAP) is allowed to bind in the presence or absence of a test sample to the immobilized FK-506. After washing (to remove non-specifically bound macrophilin), bound biot-MAP is assessed by incubation with a streptavidin-alkaline phosphatase conjugate, followed by washing and subsequent addition of p-nitrophenyl phosphate as a substrate. The read-out is the OD at 405nm. Binding of a test sample to biot-MAP results in a decrease in the amount of biot-MAP bound to the FK-506 and thus in a decrease in the OD405. A dilution series of the test sample allows determination of the concentration resulting in 50% inhibition of the biot-MAP binding to the immobilized FK-506 (IC_{50}). The exemplified Novel Compounds all exhibit good binding to FKBP in this assay.

4. Localized Graft-Versus-Host (GvH) Reaction

In vivo efficacy of the Novel Compounds is proved in a suitable animal model, as described, e.g., in Ford et al, TRANSPLANTATION 10 (1970) 258. Spleen cells (1×10^7) from 6 week old female Wistar/Furth (WF) rats are injected subcutaneously on day 0 into the left hind-paw of female (F344 x WF)F_1 rats weighing about 100g. Animals are treated for 4 consecutive days and the popliteal lymph nodes are removed and weighed on day 7. The difference in weight between the two lymph nodes is taken as the parameter for evaluating the reaction.

5. Kidney Allograft Reaction in Rat

One kidney from a female fisher 344 rat is transplanted onto the renal vessel of a unilaterally (left side) nephrectomized WF recipient rat using an end-to-end anastomosis. Ureteric anastomosis is also end-to-end. Treatment commences on the day of transplantation and is continued for 14 days. A contralateral nephrectomy is done seven days after transplantation, leaving the recipient relying on the performance of the donor kidney. Survival of the graft recipient is taken as the parameter for a functional graft.

6. Experimentally Induced Allergic Encephalomyelitis (EAE) in Rats

Efficacy of the Novel Compounds in EAE is measured, e.g., by the procedure described in Levine & Wenk, AMER J PATH 47 (1965) 61; McFarlin et al, J IMMUNOL 113 (1974) 712; Borel, TRANSPLANT. & CLIN. IMMUNOL 13 (1981) 3. EAE is a widely accepted model for multiple sclerosis. Male Wistar rats are injected in the hind paws with a mixture of bovine spinal cord and complete Freund's adjuvant. Symptoms of the disease (paralysis of the tail and both hind legs) usually develop within 16 days. The number of diseased animals as well as the time of onset of the disease are recorded.

7. Freund's Adjuvant Arthritis

Efficacy against experimentally induced arthritis is shown using the procedure described, e.g., in Winter & Nuss, ARTHRITIS & RHEUMATISM 9 (1966) 394; Billingham & Davies, HANDBOOK OF EXPERIMENTAL PHARMACOL (Vane & Ferreira Eds, Springer-Verlag, Berlin) 50/II (1979) 108-144. OFA and Wistar rats (male or female, 150g body weight) are injected i.c. at the base of the tail or in the hind paw with 0.1 ml of mineral oil containing 0.6 mg of lyophilized heat-killed Mycobacterium smegmatis. In the developing arthritis model, treatment is started immediately after the injection of the adjuvant (days 1 - 18); in the established arthritis model treatment is started on day 14, when the secondary inflammation is well developed (days 14-20). At the end of the experiment, the swelling of the joints is measured by means of a micro-caliper. ED_{50} is the oral dose in mg/kg which reduces the swelling (primary or secondary) to half of that of the controls.

8. Antitumor and MDR activity

The antitumor activity of the Novel Compounds and their ability to enhance the performance of antitumor agents by alleviating multidrug resistance is demonstrated, e.g., by administration of an anticancer agent, e.g., colchicine or etoposide, to multidrug resistant cells and drug sensitive cells in vitro or to animals having multidrug resistant or drug sensitive tumors or infections, with and without co-administration of the Novel Compounds to be tested, and by administration of the Novel Compound alone. Such in vitro testing is performed employing any appropriate drug resistant cell line and control

(parental) cell line, generated, e.g. as described by Ling et al., J. Cell. Physiol. 83, 103-116 (1974) and Bech-Hansen et al. J. Cell. Physiol. 88, 23-32 (1976). Particular clones chosen are the multi-drug resistant (e.g. colchicine resistant) line CHR (subclone C5S3.2) and the parental, sensitive line AUX B1 (subclone AB1 S11). In vivo anti-tumor and anti-MDR activity is shown, e.g., in mice injected with multidrug resistant and drug sensitive cancer cells. Ehrlich ascites carcinoma (EA) sub-lines resistant to drug substance DR, VC, AM, ET, TE or CC are developed by sequential transfer of EA cells to subsequent generations of BALB/c host mice in accordance with the methods described by Slater et al., J. Clin. Invest, 70, 1131 (1982). Equivalent results may be obtained employing the Novel Compounds test models of comparable design, e.g. in vitro, or employing test animals infected with drug-resistant and drug sensitive viral strains, antibiotic (e.g. penicillin) resistant and sensitive bacterial strains, anti-mycotic resistant and sensitive fungal strains as well as drug resistant protozoal strains, e.g. Plasmodial strains, for example naturally occurring sub-strains of Plasmodium falciparum exhibiting acquired chemotherapeutic, anti-malarial drug resistance.

9. Steroid potentiation

The macrophilin binding activity of the Novel Compounds also makes them useful in enhancing or potentiating the action of corticosteroids. Combined treatment with the compounds of the invention and a corticosteroid, such as dexamethasone, results in greatly enhanced steroidal activity. This can be shown, e.g., in the murine mammary tumor virus-chloramphenicol acetyltransferase (MMTV-CAT) reporter gene assay, e.g., as described in Ning, et al., *J. Biol. Chem.* (1993) **268**: 6073. This synergistic effect allows reduced doses of corticosteroids, thereby reducing the risk of side effects in some cases.

10. Mip and Mip-like factor inhibition

Additionally, the Novel Compounds bind to and block a variety of Mip (macrophage infectivity potentiator) and Mip-like factors, which are structurally similar to macrophilin. Mip and Mip-like factors are virulence factors produced by a wide variety of pathogens, including those of the genera Chlamidia, e.g., Chlamidia

trachomatis; Neisseria, e.g., Neisseria meningitidis; and Legionella, e.g., Legionella pneumophilia; and also by the obligately parasitic members of the order Rickettsiales. These factors play a critical role in the establishment of intracellular infection. The efficacy of the Novel Compounds in reducing the infectivity of pathogens which produce Mip or Mip-like factors can be shown by comparing infectivity of the pathogens in cells culture in the presence and absence of the macrolides, e.g., using the methods described in Lundemose, et al., *Mol. Microbiol.* (1993) 7: 777.

The Novel Compounds are also useful in assays to detect the presence or amount of macrophilin-binding compounds, e.g., in competitive assays for diagnostic or screening purposes. Thus, in another embodiment, the invention provides for use of the Novel Compounds as a screening tool to determine the presence of macrophilin-binding compounds in a test solution, e.g., blood, blood serum, or test broth to be screened. Preferably, a Novel Compound is immobilized in microtiter wells and then allowed to bind in the presence and absence of a test solution to labelled macrophilin-12 (FKBP-12). Alternatively, the FKBP-12 immobilized in microtiter wells and allowed to bind in the presence and absence of a test solution to a Novel Compound which has been labelled, e.g., fluoro-, enzymatically- or radio-labelled, e.g., a Novel Compound of Formula I wherein R_1 comprises a labelling group. The plates are washed and the amount of bound labelled compound is measured. The amount of macrophilin-binding substance in the test solution is roughly inversely proportional to the amount of bound labelled compound. For quantitative analysis, a standard binding curve is made using known concentrations of macrophilin binding compound.

The following examples are intended to illustrate rather than limit the invention. Characteristic spectrascopic data is provided to aid in identification of the compounds.

Example 1: 16-demethoxy-16-(pent-2-ynyl)oxy-rapamycin

To a solution of 0.6 ml 2-pentyn-1-ol in 5 ml CH_2Cl_2 are added 456 mg rapamycin followed by 5 mg p-toluenesulfonic acid. The mixture is stirred for 2 h at room temperature. Then the reaction is quenched with 7 ml of a saturated aqueous solution of

$NaHCO_3$. The aqueous phase is separated and extracted 2x with 10 ml ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over silica gel, eluting with ethyl acetate/hexane 3/2. The crude product is finally purified by preparative HPLC (RP-18, 250x10 mm, MeOH/H2O 80/20, 3 ml/min).

MS (FAB) m/z 972 (M+Li)

H-NMR (CDCl3)(major isomer) d: 0.67 (1H, q); 1.13 (3H, t); 1.67 (3H,s); 1.74 (3H, s); 3.33 (3H, s); 3.40 (3H, s); 3.73 (1H, d); 3.77 (1H, dm); 4.01 (1H, dm); 4.16 (1H, d); 4.66 (1H, s).

Example 2: 16-demethoxy-16-(but-2-ynyl)oxy-rapamycin

To a solution of 0.4 ml 2-butyn-1-ol in 3 ml CH_2Cl_2 are added 251 mg rapamycin followed by 4 mg p-toluenesulfonic acid. The mixture is stirred for 2 h at room temperature. Then the reaction is quenched with 7 ml of a saturated aqueous solution of NaHCO3. The aqueous phase is separated and extracted 2x with 10 ml ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over silica gel, eluting with ethyl acetate/hexane 3/2. The crude product is finally purified by preparative HPLC (RP-18, 250x10 mm, MeOH/H2O 80/20, 3 ml/min).

MS (FAB) m/z 958 (M+Li)

H-NMR (CDCl3)(major isomer) d: 0.67 (1H, q); 1.67 (3H,s); 1.74 (3H, s); 1.83 (1H, bs); 3.33 (3H, s); 3.40 (3H, s); 3.72 (1H, d); 3.75 (1H, dm); 4.01 (1H, dm); 4.16 (1H, d); 4.73 (1H, s).

Example 3: 16-demethoxy-16-(propargyl)oxy-rapamycin

To a solution of 0.3 ml propargyl alcohol in 3 ml CH_2Cl_2 are added 251 mg rapamycin followed by 4 mg p-toluenesulfonic acid. The mixture is stirred for 2 h at room temperature. Then the reaction is quenched with 7 ml of a saturated aqueous solution of NaHCO3. The aqueous phase is separated and extracted 2x with 10 ml ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over silica gel, eluting with ethyl

acetate/hexane 3/2. The crude product is finally purified by preparative HPLC (RP-18, 250x10 mm, MeOH/H2O 80/20, 3 ml/min).

MS (FAB) m/z 944 (M+Li)

H-NMR (CDCl3)(major isomer) d: 0.68 (1H, q); 1.66 (3H,s); 1.74 (3H, s); 2.32 (1H, bt); 3.34 (3H, s); 3.41 (3H, s); 3.67 (1H, d); 3.83 (1H, dm); 4.08 (1H, dm); 4.16 (1H, d); 4.84 (1H, s).

Example 4: 16-demethoxy-16-(4-hydroxy-but-2-ynyl)oxy-rapamycin

To a suspension of 940 mg 2-butyn-1,4-diol in 6 ml CH_2Cl_2 are added 502 mg rapamycin followed by 5 mg p-toluenesulfonic acid. The mixture is stirred for 2 h at room temperature. Then the reaction is quenched with 10 ml of a saturated aqueous solution of $NaHCO_3$. The aqueous phase is separated and extracted 2x with 10 ml ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over silica gel, eluting with ethyl acetate/hexane 4/1. The crude product is finally purified by preparative HPLC (RP-18, 250x25 mm, MeOH/H2O 75/25, 7 ml/min).

MS (FAB) m/z 974 (M+Li)

H-NMR (CDCl3)(major isomer) d: 0.67 (1H, q); 1.67 (3H,s); 1.75 (3H, s); 3.33 (3H, s); 3.41 (3H, s); 3.73 (1H, d); 3.81 (1H, dm); 4.08 (1H, dm); 4.17 (1H, d); 4.28 (2H, bs); 4.67 (1H, s).

Example 5: 16-demethoxy-16-benzyloxy-40-O-(2-hydroxyethyl)-rapamycin

To a solution of 0.6 ml benzyl alcohol in 3 ml CH_2Cl_2 are added 264 mg 40-O-(2-hydroxyethyl)-rapamycin (prepared as described in WO 94/09010) followed by 5 mg p-toluenesulfonic acid. The mixture is stirred for 1 h at room temperature. Then the reaction is quenched with 7 ml of a saturated aqueous solution of $NaHCO_3$. The aqueous phase is separated and extracted 2x with 10 ml diethyl ether. The organic phases are combined, dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over silica gel, eluting with ethyl hexane/acetone 4/1 followed by hexane/acetone 1/1. The crude product is finally purified by preparative HPLC (RP-18, 250x25 mm, CH3CN/H2O 75/25, 8 ml/min).

MS (FAB) m/z 1040 (M+Li)

H-NMR (CDCl3)(major isomer) d: 0.72 (1H, q); 1.73 (6H,s); 3.32 (3H, s); 3.43 (3H, s); 3.7 (4H, m); 4.15 (1H, d); 4.18 (1H, d); 4.47 (1H, d)); 4.80 (1H, s); 7.3 (5H, m).

Example 6: 16-demethoxy-16-benzyloxy-rapamycin:

1 mmol rapamycin is dissolved in 50 ml methylene chloride containing 3 ml of benzyl alcohol. 0.1 mmol of p-toluenesulphonic acid is added, and the reaction mixture is then stirred at room temperature for 2-10 hours. The reaction mixture is then poured in a saturated solution of sodium bicarbonate. The organic layer is separated, dried over sodium sulphate, and the solvent evaporated. The crude product is then purified by HPLC to give the pure title compound as a white powder.

Example 7: 16-demethoxy-16-(*ortho*-methoxybenzyl)oxy-rapamycin

To a solution of 0.76 g of *ortho*-methoxy-benzyl alcohol in 3 mL CH_2Cl_2 are added 250 mg of rapamycin followed by 5 mg of p-toluenesulfonic acid. The mixture is stirred for 8 h at room temperature and the reaction is quenched with 5 mL of a saturated aqueous solution of $NaHCO_3$. The layers are separated and the aqueous layer is extracted 2x with 10 mL ether. The combined organic solution is dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is chromatographed over silica gel, using hexane/acetone (4/1 to 3/2) as the eluent. The resulting product is further purified by preparative HPLC (RP-18, 250x25 mm, CH_3CN/H_2O 75/25, 8 mL/min).

MS (FAB) m/z 1026 (M+Li)

H-NMR ($CDCl_3$) (major isomer) δ: 0.67 (1H, q); 1.73 and 1.74 (6H, 2s); 3.33 (3H, s); 3.41 (3H, s); 3.72 (1H, d); 3.81 (3H, s); 4.18 (1H, broad d); 4.26 (1H, d); 4.45 (1H, d); 4.72 (1H, broad s); 6.83 (1H, d); 6.92 (1H, m); 7.23 (1H, m); 7.32 (1H, m).

Example 8: 16-demethoxy-40-O-(2-methoxyethyl)-16-(pent-2-ynyl)oxy-rapamycin

To a solution of 0.7 ml 2-pentyn-1-ol in 5 ml CH_2Cl_2 are added 486 mg of 40-O-(2-methoxyethyl)-rapamycin followed by 5 mg p-toluenesulfonic acid. The mixture is stirred for 2 h at room temperature. Then the reaction is quenched

with 7 ml of a saturated aqueous solution of $NaHCO_3$. The aqueous phase is separated and extracted 2x with 10 ml ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over silica gel, eluting with ethyl acetate/hexane 1/1. The crude product is finally purified by preparative HPLC (RP-18, 250x25 mm, MeOH/H2O 83/17, 7 ml/min).

MS (FAB) m/z 1030 (M+Li)

H-NMR (CDCl3)(major isomer) d: 0.72 (1H, q); 1.14 (3H, t); 1.67 (3H,s); 1.74 (3H, s); 3.33 (3H, s); 3.38 (3H, s); 3.45 (3H, s); 3.73 (1H, d); 3.77 (1H, dm); 4.01 (1H, dm); 4.17 (1H, d); 4.65 (1H, s).

Example 9: 39-demethoxy-40-desoxy-39-formyl-42-nor-rapamycin

To a solution of 1.85 g of rapamycin in 40 ml acetonitrile at -30 C are added 365 µl morpholinosulphur trifluoride. The reaction mixture is kept 1h at -30 C, 1h at 0 C and then quenched with a saturated aqueous bicarbonate solution. The aqueous phase is extracted 3x with 30 ml ethyl acetate, and the organic phases are combined and dried over sodium sulfate. After evaporation of the solvent, the crude product is purified by column chromatography over silica gel, eluting with hexane/acetone 4/1.

MS (FAB, LiI matrix) : 888 (M+ Li)

H-NMR (CDCl3): 3.13 (s, 3H); 3.34 (s, 3H); 9.62 (d, 1H); no other singulet between 3.0 and 3.6 ppm. No signal between 0.6 and 0.85 ppm

Example 10: 39-demethoxy-40-desoxy-39-hydroxymethyl-42-nor-rapamycin

A solution of 44 mg 39-demethoxy-40-desoxy-39-formyl-42-nor-rapamycin in 1.2 ml of THF/water 5/1 is treated with 1.5 mg of t-butylamine/borane complex for 2h at 0 C. the reaction mixture is then poured on 2 ml HCl 0.1N and extracted with 3x 5 ml ethyl acetate. The organic phases are combined, washed with 2 ml of a saturated sodium bicarbonate solution and dried over sodium sulfate. The solvent is evaporated in vacuo, and the crude product is purified by column chromatography over silica gel eluting with hexane/ethyl acetate 1/1.

MS (FAB, LiI matrix): 890 (M + Li)

H-NMR (CDCl3): 3.13 (s, 3H); 3.33 (s, 3H); 4.18 (m, 2H). No signal betwwen 0.5 and 0.85 ppm.; no aldehyde proton at 9.62 ppm.

Example 11: 39-demethoxy-40-desoxy-39-carboxy-42-nor-rapamycin

A solution of 85 mg NaOCl and 113 mg NaH_2PO_4 in 2 ml water is added to a solution of 111 mg 39-demethoxy-40-desoxy-39-formyl-42-nor-rapamycin and 0.2 ml 2-methyl-2-butene in 4 ml t-butanol. The mixture is stirred at room temperature for 2h. The solvents are then evaporated and the residue extracted with 3x 5 ml ethyl acetate. The organic phases are combined, dried over anhydrous sodium sulfate and the solvent evaporated. The product is purified by preparative HPLC (RP-18, 250x10 mm, acetonitrile/water 60/40, 3 ml/mn).

MS (FAB, LiI matrix): 904 (M+Li)

H-NMR(CDCl3): 1.65(s, 3H); 1.78(s, 3H); 3.13(s, 3H); 3.33(s, 3H); 3.75(d, 1H); 4.18 (d, 1H). No signal below 0.85 ppm. No additional singulet in the region 3.0-3.6 ppm.

Example 12:

39-demethoxy-40-desoxy-39-(4-methyl-piperazin-1-yl)carbonyl-42-nor-rapamycin

To a stirred solution of 180 mg 39-carboxy-39-demethoxy-40-desoxy-42-nor-rapamycin in 4 ml THF at - 75 C are added 0.08 ml pyridine followed by 0.04 ml oxalyl chloride. The reaction mixture is kept at - 75 C for 30 minutes after which 0.09 ml N-methyl-piperazine are added. The reaction is stirred for an additional hour and then quenched with 5 ml of saturated aqueous sodium bicarbonate and 5 ml ethyl acetate. The water phase is separated and extracted with 2x 5 ml ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent evaporated. The crude product is purified by preparative HPLC (RP-18, 250x10 mm, MeOH/H2O 85/15, 3 ml/mn).

MS (FAB) m/z 986 (M+Li)

H-NMR (CDCl3) d= 1.65 (3H, s); 1.78 (3H, s); 2.31 (3H, s); 2.4 (4H, m); 3.13 (3H, s); 34 (3H, s); 3.79 (1H, d); 4.21 (1H, d); 4.68 (1H, bs).

Example 13: 39-demethoxy-40-desoxy-39-(morpholin-4-yl)carbonyl-42-nor-rapamycin

This compound is obtained following the method of Example 11, using morpholine instead of N-methyl-piperazine.

MS (FAB) m/z 973 (M+Li)

H-NMR (CDCl3) d= 1.65 (3H, s); 1.77 (3H, s); 3.13 (3H, s); 3.33 (3H, s); 3.6 (4H, m); 3. 77 (1H, d); 4.19 (1H, d); 4.66 (1H, bs).

Example 14: 39-demethoxy-40-desoxy-39-[N-methyl,N-(2-pyridin-2-yl-ethyl)]carbamoyl-42-nor-rapamycin

This compound is obtained following the method of Example 11 using (2-pyridin-2-yl-ethyl)methylamine instead of N-methyl-piperazine.

MS (FAB) m/z 1022 (M+Li)

H-NMR (CDCl3) d= 1.66 (3H, s); 1.78 (3H, s); 2.93 (3H, s); 3.13 (3H, s); 3.33 (3H, s); 4.23 (1H, m); 4.67 (1H, s); 7.1 (2H, m); 7.6 (1H, m); 8.51 (1H, d).

Example 15:

39-demethoxy-40-desoxy-39-(p-toluenesulfonylhydrazonomethyl)-42-nor-rapamycin

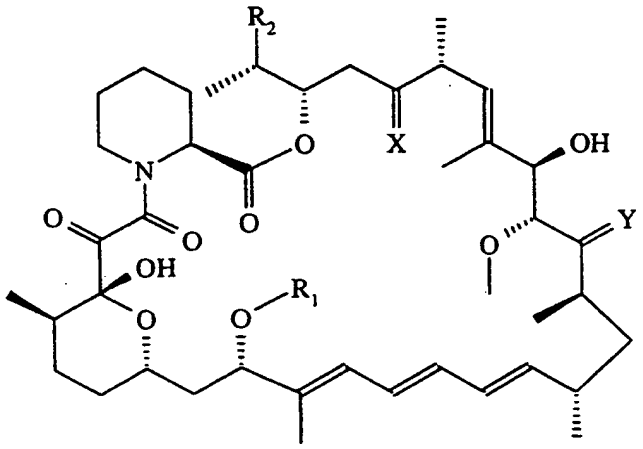
To a mixture of 523 mg 39-demethoxy-40-desoxy-39-formyl-42-nor-rapamycin in 10 ml acetonitrile are added 156 mg p-toluenesulfonylhydrazide. The reaction mixture is stirred for 30 minutes at room temperature and then the solvent is evaporated. The residue is chromatographed over silica gel, eluting with hexane/acetone 5/1, to give the title compound.

MS (FAB) m/z 1056 (M+Li)

H-NMR (CDCl3) d= 1.65 (3H, s); 1.76 (3H, s); 2.43 (3H, s); 3.13 (3H, s); 3.34 (3H, s); 3.79 (1H, d); 4.18 (1H, d); 4.69 (1H, bs); 7.13 (1H, d); 7.32 (2H, d); 7.56 (1H, s); 7.80 (2H, d).

CLAIMS

1. A compound of Formula I:

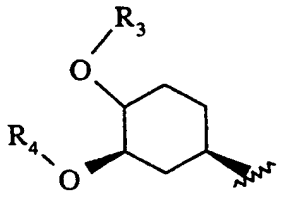


Formula I

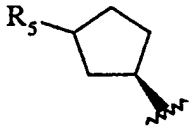
wherein

R_1 is selected from alkyl, alkenyl, alkynyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, aryl, thioalkyl, arylalkyl, hydroxyarylalkyl, hydroxyaryl, dihydroxyalkyl, hydroxyalkoxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, alkoxyarylalkyl, haloalkyl, haloaryl. haloarylalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylamidoalkyl, acylamidoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and alkylsilyl;

R_2 is selected from formula II or formula III:



Formula II



Formula III

wherein

R_3 is selected from H, alkyl, alkyenyl, alkynyl, aryl, thioalkyl, arylalkyl, hydroxyarylalkyl, hydroxyaryl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkoxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylamidoalkyl, acylamidoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and alkylsilyl;

R_4 is H, methyl or together with R_3 forms C_{2-6} alkylene;

R_5 is substituted or unsubstituted acyl, oxymethyl, iminomethyl, or dioxymethylyne;

wherein "alk" or "alkyl" refers to a C_{1-10} aliphatic substituent (branched, linear, or cyclic), optionally interrupted by an oxy (-O-) linkage; and "ar" or "aryl" refers to a monocyclic, optionally heterocyclic, optionally substituted, C_{4-14} aromatic substituent;

provided that when R_2 is of formula II, then R_1 is other than methyl and (i) R_3 is selected from hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, and aminoalkyl; and/or (ii) X is other than O; and/or (iii) R_1 is (optionally hydroxy-substituted) alkynyl;

and further provided that when R_1 is methyl, R_2 is of Formula III.

2. A compound according to claim 1 of Formula I wherein R_1 is selected from benzyl, *ortho*-alkoxybenzyl, chlorobenzyl, and (optionally hydroxy-substituted) alkynyl; R_2 is of formula II; R_3 is selected from H, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, and aminoalkyl; R_4 is methyl; and X and Y are independently selected from O, (H,OH), and (H, C_{1-4}alkoxy);

3. A compound according to claim 2 of Formula I wherein R_1 is (optionally hydroxy-substituted) C_{3-6} alk-2-ynyl; R_2 is of formula II; R_3 is selected from H, hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl; R_4 is methyl; and X and Y are O;

4. A compound according to claim 1 of Formula I wherein R_2 is of Formula III.

5. A compound according to claim 1 selected from

i. 16-demethoxy-16-(pent-2-ynyl)oxy-rapamycin
ii. 16-demethoxy-16-(but-2-ynyl)oxy-rapamycin
iii. 16-demethoxy-16-(propargyl)oxy-rapamycin
iv. 16-demethoxy-16-(4-hydroxy-but-2-ynyl)oxy-rapamycin
v. 16-demethoxy-16-benzyloxy-40-O-(2-hydroxyethyl)-rapamycin
vi. 16-demethoxy-16-benzyloxy-rapamycin
vii. 16-demethoxy-16-*ortho*-methoxybenzyl-rapamycin
viii. 16-demethoxy-40-O-(2-methoxyethyl)-16-(pent-2-ynyl)oxy-rapamycin
ix. 39-demethoxy-40-desoxy-39-formyl-42-nor-rapamycin
x. 39-demethoxy-40-desoxy-39-hydroxymethyl-42-nor-rapamycin
xi. 39-demethoxy-40-desoxy-39-carboxy-42-nor-rapamycin
xii. 39-demethoxy-40-desoxy-39-(4-methyl-piperazine-1-carbonyl)-42-nor-rapamycin
xiii. 39-demethoxy-40-desoxy-39-(morpholin-4-yl)carbonyl-42-nor-rapamycin
xiv. 39-demethoxy-40-desoxy-39-[N-methyl,N-(2-pyridin-2-yl-ethyl)]carbamoyl-42-nor-rapamycin
xv. 39-demethoxy-40-desoxy-39-(p-toluenesulfonylhydrazonomethyl)-42-nor-rapamycin

6. A compound according to any one of claims 1 through 5 for use as a pharmaceutical.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 through 4 together with a pharmaceutically acceptable diluent or carrier.

8. Use of a compound according to any one of claims 1 through 4 in the manufacture of a medicament for treating or preventing any of the following conditions:

(i) autoimmune disease,
(ii) acute rejection of organ or tissue transplant,
(iii) hyperacute rejection of organ or tissue transplant,
(iii) chronic rejection of organ or tissue transplant,
(iii) graft vs. host disease,
(iv) asthma,
(v) multidrug resistance,
(vi) tumors or hyperproliferative disorders, or
(vii) fungal infections,
(viii) inflammation, or
(ix) infection by pathogens having Mip or Mip-like factors.

9. A process for making a compound of Formula I comprising one or more of the following steps:

i. When the compound desired is for Formula I wherein R_1 is other than methyl, reacting rapamycin or a derivative thereof with SeO_2 and a compound R_1-OH under suitable reaction conditions, wherein R_1 is as defined as for Formula I, or reacting rapamycin or a derivative thereof with an acid and a compound R_1-OH in a suitable aprotic solvent;

ii. When the compound desired is of formula I where R_2 is of formula II and R_3 is other than H, reacting rapamycin or a derivative thereof with an organic radical attached to a leaving group R_3-Z where R_3 is an organic radical as defined in Formula I which is desired as the O-substituent, and Z is the leaving group (preferably $CCl_3C(NH)O$ or CF_3SO_3) in the presence of a suitable acid, e.g., when Z is $CCl_3C(NH)O$, or in the presence of a suitable base, e.g., when Z is CF_3SO_3;

iii. When the compound desired is of formula I where R_2 is of formula III, reacting rapamycin or a derivative thereof with morpholinosulphur trifloride to obtain the aldehyde compound, then optionally oxidizing the aldehyde to the carboxylic acid or

reducing the aldehyde to the corresponding alcohol; and further optionally (a) O-substituting the alcohol thus obtained, as in step ii, or (b) reacting the carboxylic acid thus obtained with an amine or alcohol in the presence of an activating or coupling reagent to give the desired amide or ester compounds respectively, or (c) condensing the aldehyde thus obtained with the desired amine or alkylenediol, respectively, under acidic conditions to obtain the iminomethyl or dioxymethylyne compounds respectively;

iv. When the compound desired is of formula I where X is other than O, reducing a rapamycin or derivative (in O-protected form) at the 32-keto to obtain the alcohol and optionally further O-substituting as in step ii;

v. Optionally protecting and deprotecting as necessary;

and recovering the compound of Formula I thus obtained.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 94/04191

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D498/18 A61K31/395 C07F7/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US,A,5 310 903 (GOULET) 10 May 1994 see claim 1	1-9
P,X	US,A,5 310 901 (PARSONS) 10 May 1994 see claim 1	1-9
P,X	WO,A,94 09010 (SANDOZ) 28 April 1994 cited in the application see claim 1	1-9
X	US,A,5 262 423 (KAO) 16 November 1993 see claim 1	1-9
X	US,A,5 258 389 (GOULET) 2 November 1993 cited in the application see claim 1	1-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 1995	0 9. 05. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Gettins, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US,A,5 151 413 (CAUFIELD) 29 September 1992 cited in the application see claim 1	1-9
X	US,A,5 120 842 (FAILLI) 9 June 1992 cited in the application see claim 1	1-9
X	US,A,5 118 678 (KAO) 2 June 1992 cited in the application see claim 1	1-9
X	US,A,5 118 677 (CAUFIELD) 2 June 1992 cited in the application see claim 1	1-9
X	WO,A,92 05179 (AMERICAN HOME PRODUCTS CORPORATION) 2 April 1992 cited in the application see claim 1	1-9
X	US,A,5 100 883 (SCHIEHSER) 31 March 1992 cited in the application see claim 1	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 94/04191

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US-A-5258389	02-11-93	NONE		
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		AU-A-	8659991	15-04-92
		CA-A-	2051781	20-03-92
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		HU-A-	65763	28-07-94
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		NZ-A-	242778	26-07-94
WO-A-9205179	02-04-92	AU-B-	653175	22-09-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 94/04191

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		JP-T-	6501012	27-01-94
		US-A-	5358944	25-10-94
		US-A-	5378696	03-01-95
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		CA-A-	2051782	29-03-92
		US-A-	5130307	14-07-92
US-A-5100883	31-03-92	NONE		

1996

Therapeutic Immunology

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APPENDIX E

Therapeutic Approach to Organ Transplantation

Terry B. Strom and
Manikkam Suthanthiran

Organ transplantation is firmly established as the preferred treatment for many patients suffering from end-stage renal, cardiac, pulmonary, or liver disease or insulin-dependent diabetes mellitus. Nonetheless, no absolute consensus has developed on how to achieve optimal immunosuppression, and many individual centers using somewhat different protocols report excellent graft and patient survival.

Immunologic considerations, including antirejection therapy, are organized around a few general principles. The first consideration is careful patient preparation, and, in the circumstance of renal transplantation, selection of the best available ABO-compatible, human leukocyte antigen (HLA) match in the event that several potential living donors are available for organ donation. Second is a multitiered approach to immunosuppressive therapy similar in principle to that used in chemotherapy; several agents are used simultaneously, each of which is directed at a different molecular target within the allograft response (Fig 36.1, Table 36.1). Additive-synergistic effects are achieved through application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect. Third is the principle that higher immunosuppressive drug doses or more individual immunosuppressive drugs are required to gain early engraftment and to treat established rejection than are needed to maintain immunosuppression in the long term. Hence, intensive induction and lower dose maintenance drug protocols are used. Fourth is careful investigation of each episode of post-transplantation graft dysfunction, with the realization that most of the common causes of graft dysfunction, including rejection, can (and frequently do) coexist. Successful therapy, therefore, often involves several simultaneous therapeutic maneuvers. The fifth principle involves the appropriate reduction or withdrawal of an immunosuppressive drug when that drug's toxicity exceeds its therapeutic benefit.

PRETRANSPLANTATION TRANSFUSIONS

Although pretransplantation random whole blood transfusion was a powerful adjunct to transplant therapy when cyclosporine was not available, the short-term benefits of random transfusion have recently been more difficult to demonstrate in the cyclosporine era. There is no agreement concerning the role of donor-specific transfusions (DST) for recipients of HLA-mismatched living, related donor renal transplants. Occasionally, DST produces adverse presensitization to the donor. Because these sensitized patients cannot undergo transplantation with tissues procured from the transfusion donor, many units do not use routine DST. Owing to the powerful tolerizing effects of DST in experimental models, there are several active clinical trials evaluating various forms of pre- and perioperative donor blood element infusions into graft recipients as a therapeutic modality.

THERAPY DESIGNED TO PREVENT REJECTION

Antirejection protocols are aimed at interrupting several discrete stages in the immune activation pathway, leading to allograft rejection (1–3). When possible, selection is undertaken using HLA matching to minimize histoincompatibility between donor and recipient (4, 5). All post-transplantation immunosuppressive protocols use at least two agents, each directed at a discrete site in the T-cell activation cascade (see Fig 36.1, Table 36.1).

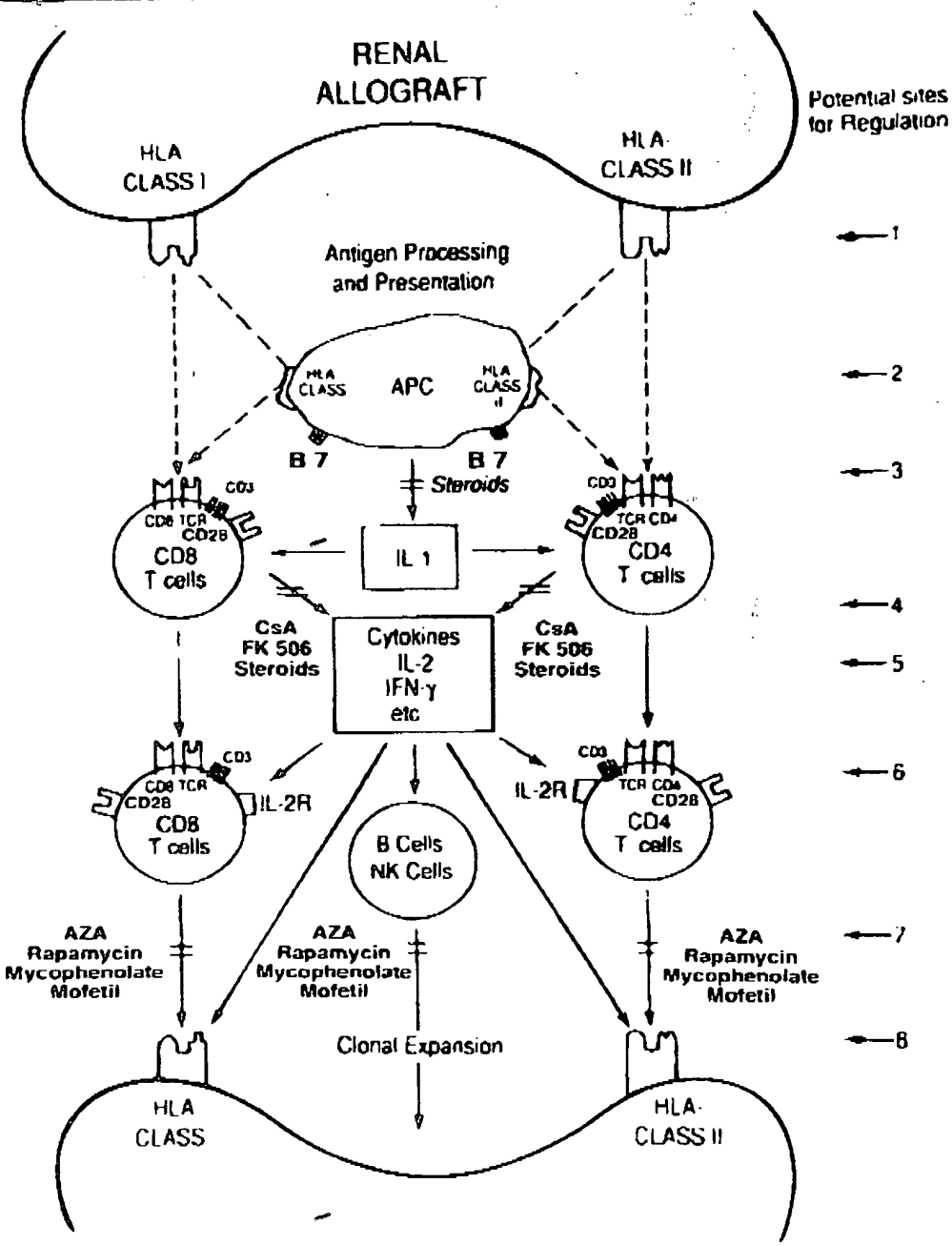

FIGURE 36.1 *The antiallograft response. Schematic representation of human leukocyte antigen (HLA), the primary stimulus for the initiation of the antiallograft response; cell surface proteins participating in antigenic recognition and signal transduction; contribution of the cytokines and multiple cell types to the immune response; and the potential sites for the regulation of the antiallograft response. Site 1: minimizing histoincompatibility between the recipients and the donor (e.g., HLA matching); site 2: prevention of monokine production by antigen-presenting cells (APCs) (e.g., corticosteroids); site 3: blockade of antigen recognition (e.g., OKT3 monoclonal antibodies); site 4: inhibition of T-cell cytokine production (e.g., cyclosporine [CsA]); site 5: inhibition of cytokine activity (e.g., anti-interleukin [IL]-2 antibody); site 6: inhibition of cell cycle progression (e.g., anti-IL-2 receptor antibody); site 7: inhibition of clonal expansion (e.g., azathioprine); site 8: prevention of allograft damage by masking target antigen molecules (e.g., antibodies directed at adhesion molecules). (HLA-class 1 = HLA-A, B, and C antigens; HLA-class 2 = HLA-DR and DQ antigens; AZA = azathioprine; IFN-γ = interferon-γ; NK = natural killer; TCR = T-cell receptor.)*

Table 36.1. Mechanism of Action of Immunosuppressants

AGENT	MODE OF ACTION
Cyclosporine-FK506	Blocks Ca^{2+}-dependent T-cell activation pathway via binding to calcineurin
Corticosteroids	Blocks cytokine gene expression
Azathioprine	Inhibits purine synthesis
Mycophenolate mofetil	Inhibits a lymphocyte-specific guanosine synthesis pathway
Rapamycin	Inhibits the response of antigen-activated lymphocytes to growth factors

IMMUNOPHARMACOLOGY OF ALLOGRAFT REJECTION

Cyclosporine and tacrolimus (FK506)

Cyclosporine, a small neutral hydrophobic cyclic peptide of fungal origin, and tacrolimus (FK506), a water-soluble macrolide lactone produced by *Streptomyces tsukubaenis*, block the Ca^{2+}-dependent T-cell activation pathway (6–9). Oral doses of both agents are erratically absorbed. Insofar as absorption of cyclosporine, but not FK506, requires bile, the absorption of FK506 is not influenced by clamping a T-tube. In this limited respect, treatment of liver transplant recipients with FK506 provides superior bioavailability. The immunosuppressive effects of cyclosporine and FK506 are dependent on the formation of heterodimeric complexes that consist of the native compound (cyclosporine or FK506) and its respective cytoplasmic "immunophilin" receptor protein, cyclophilin (10) or FK-binding protein (FKBP) (11, 12). Both cyclosporine-cyclophilin and FK506-FKBP complexes bind calcineurin, a calcium- and calmodulin-sensitive phosphatase, and inhibit its enzymatic activity (see Fig 36.1; Table 36.1) (13–15). Cyclosporine-FK506–mediated inhibition of calcineurin's phosphatase activity prevents the dephosphorylation of cytoplasmic NF-AT and thereby impedes subsequent import of this deoxyribonucleic acid (DNA)-binding protein into the nucleus (7, 8). Cyclosporine-FK506 inhibits the expression of not only NF-AT (16, 17) but also the activities of other DNA-binding proteins such as NF-kB and activated protein-1 (AP-1) factors (18–20). The phosphorylation status of transcription factors affects not only their nuclear import but also their DNA-binding ability and interaction with the cellular transcriptional machinery (e.g., c-*jun*) (21).

Cyclosporine-FK506 inhibits activation of several cytokine genes, including the interleukin (IL)-2, IL-4, and interferon (IFN)-γ genes; however, this activity does not totally account for the antiproliferative effect of cyclosporine-FK506 on activated T cells. Inhibition of expression of proto-oncogenes (e.g., H-*ras*, c-*myc*) as well as prevention of expression of receptors for cytokines (e.g., the IL-2 alpha chain receptor) might also be quite important in this regard (22, 23).

It is also significant that cyclosporine, in striking contrast to its inhibitory activity on the induced expression of IL-2, enhances the expression of transforming growth factor-β (TGFβ) (24). Because TGFβ is a potent inhibitor of IL-2–stimulated T-cell proliferation and generation of antigen-specific cytotoxic T lymphocytes, enhanced expression of TGFβ is likely to contribute to the immunosuppressive activity of cyclosporine. This novel effect of cyclosporine suggests also a mechanism for some of the complications (e.g., renal fibrosis) of cyclosporine therapy since TFGβ is a fibroblast growth factor (25).

Corticosteroids

Corticosteroids were first used in clinical transplantation to reverse acute rejection reactions in patients treated with maintenance doses of azathioprine. It is now customary to use modest doses of a corticosteroid in maintenance protocols that also use cyclosporine or tacrolimus with or without azathioprine. A short course of high doses of corticosteroids is often used to treat acute rejection episodes. Corticosteroids inhibit T-cell proliferation, T-cell–dependent immunity, and cytokine gene transcription (including IL-1, IL-2, IL-6, IFNγ, and tumor necrosis factor-α genes) (see Fig 36.1, Table 36.1) (26–28). Although no individual cytokine can totally reverse the inhibitory effects of corticosteroids on mitogen-stimulated T-cell proliferation, a combination of cytokines is effective (29).

Some cytokine genes possess a glucocorticosteroid response element in the 5' regulatory region that serves as a target for the heterodimeric complex formed by the association of corticosteroids with the intracellular glucocorticosteroid receptor protein. Binding of this complex to the glucocorticosteroid response element can, in theory, block gene expression. Blockade of IL-2 gene transcription, however, involves impairment of the cooperative effect of several DNA-binding proteins (30), although the IL-2 gene does not possess a glucocorticosteroid response element.

There are several additional mechanisms by which glucocorticoids might block T-cell activation. Glucocorticoids can block expression of numerous genes through the noncovalent association of the interaction of the activated hormone-receptor complex with the c-*jun*/c-*fos* heterodimer (AP-1) (31); c-*jun* and

terized by a dense infiltration of T cells in the medullary regions of the graft. We often treat the first kidney allograft rejection episode with 1 gm of intravenous methylprednisolone daily for 3 consecutive days. The mechanism by which corticosteroids act to reduce the intensity of leukocytic infiltration in a rejecting allograft has not been fully elucidated; however, release of numerous cytokines is blocked by high-dose steroids, and T-cell trafficking patterns are altered.

OKT3-treated T cells lose their antigen receptor proteins and become literally blinded to the presence of the allograft; thus, rejection abates. OKT3 is superior to standard high-dose corticosteroid therapy for reversing kidney allograft rejection (90% versus 70% success) (40). More than 90% of first rejections and a high percentage of second rejections respond to OKT3 therapy. Nonetheless, OKT3 is often reserved as treatment for corticosteroid-resistant rejection episodes. As antirejection treatment, OKT3 is given as a daily 5-mg intravenous bolus for 5 to 10 consecutive days.

Although prophylactic administration of OKT3 to patients in the immediate post-transplantation period is well tolerated, administration of the first and occasionally second dose of OKT3 to patients treated for ongoing rejection often causes a "capillary leak" syndrome that can lead to severe adult respiratory distress syndrome–type pulmonary edema, hypotension, or aseptic meningitis (1, 2, 44). This syndrome is caused by the release of lymphokines from the OKT3-targeted activated T cells. Because of these troublesome symptoms as well as additional expense, we reserve OKT3 therapy for steroid-insensitive rejection episodes. Subsequent doses are well tolerated. Approximately 75% of patients develop immunoglobulin (Ig)G or IgM anti-idiotype or anti-isotype antibodies against OKT3. Azathioprine at doses of 1 to 2 mg/kg/day and prednisone at 30 mg/day are used to limit the frequency and delay the onset of occurrence of host anti-OKT3 antibodies. OKT3 is not efficacious in patients who have developed high-titer anti-idiotypic antibodies against OKT3. Anti-isotypic antibodies do not neutralize the immunosuppressive properties of OKT3.

Polyclonal or antilymphocyte antibody preparations are derived from animals immunized with human lymphocytes. The antibodies are directed against both lymphocyte-specific antigens and more broadly expressed antigens. More than 80% of steroid-resistant first rejection episodes will respond to these polyclonal antibodies. Patients are skin tested with 0.1 mg of a 1:1000 dilution of polyclonal antilymphocyte antibodies before administration of the first dose and pretreated before each dose with diphenhydramine and steroids. Antilymphocyte antibodies, often at a dosage of 10 to 15 mg/kg, are administered daily by slow intravenous infusion over 4 to 8 hours for 10 to 14 days. Adverse reactions include anaphylaxis, hemolysis, thrombocytopenia, neutropenia, dyspnea, chills, fever, hypotension, chemical phlebitis, pruritus, serum sickness, and chest, flank, and back pain. Unlike the complications noted with the first dose of OKT3, the severity of anaphylactoid side effects to these polyclonal antilymphocyte preparations can increase with subsequent doses. Frank anaphylaxis can occur anytime during treatment. The use of polyclonal antilymphocyte antibodies has decreased in the United States because OKT3 is less toxic and comparably effective in reversing rejection.

We rarely treat a kidney transplant recipient for more than three rejection episodes in the early post-transplantation period because third and fourth rejections tend to be vasculitic forms that are therapeutically resistant, and the risks to the patient from zealous immunosuppression are unacceptably high by that point. In contrast, patients with cardiac allografts who will die with the cessation of cardiac function are treated more vigorously because complete rejection, in the absence of retransplantation, is fatal.

Although current drug protocols are far superior to those used a decade ago, the situation is far from ideal. Most allografts eventually succumb to chronic rejection. Long-term therapy is mandatory. We anticipate clinical application, in the near future, of more refined immunosuppressive regimens: new drugs, humanized mAbs, and fusion proteins that target discrete steps in antigen recognition, signal transduction, and effector immunity. We are also optimistic regarding the inducibility of antigen-specific tolerance in the clinical setting, but a delivery date cannot yet be guaranteed.

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LEXSEE 837 F.2D 469

In Re Dow Chemical Co.

No. 87-1406

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

837 F.2d 469; 1988 U.S. App. LEXIS 587; 5 U.S.P.Q.2D (BNA) 1529

January 25, 1988, Decided

PRIOR HISTORY: [**1]

Appealed from: United States Patent and Trademark Office Board of Patent Appeals and Interferences.

CASE SUMMARY:

PROCEDURAL POSTURE: Appellant challenged the order of the United States Patent and Trademark Office Board of Patent Appeals and Interferences, rejecting on reexamination all claims of appellant's patent application.

OVERVIEW: Appellant challenged the order of the appeals board rejecting all the claims of appellant's patent application, which based its decision on the contention that the claimed invention would have been obvious in terms of *35 U.S.C.S § 103.* Appellant argued that the board erred when it engaged in hindsight reconstruction of the claimed invention and combined prior art teachings when no reference showed or suggested that references should or could be combined successfully. The court found that the evidence as a whole did not support the board's conclusion that the claimed invention would have been obvious in terms of *35 U.S.C.S. § 103,* and that the board applied an incorrect "obvious to experiment" standard to its determination.

OUTCOME: The court reversed the board's rejection of appellant's patent application because it found that the evidence as a whole did not support the board's conclusion that the claimed invention would have been obvious, and the board applied an incorrect "obvious to experiment" standard to its determination.

CORE TERMS: rubber, anhydride, maleic, invention, styrene, diene, polymer, synthetic, resin, copolymer, alkenyl, inventors, patent, skill, natural rubber, phase, aromatic, monomer, obviousness, nonequimolar, high-impact, resistance, disclosure, inversion, moldable, improved, desired, react, heat, patentability

LexisNexis(R) Headnotes

Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness
Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN1] Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness.

Patent Law > Nonobviousness > Elements & Tests > Manner of Conception
[HN2] See *35 U.S.C.S. § 103.*

Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN3] The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.

Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard

Patent Law > Nonobviousness > Elements & Tests > Claimed Invention as a Whole

[HN4] In determining whether a suggestion of obviousness can fairly be gleaned from the prior art, the full field of the invention must be considered, for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.

Patent Law > Nonobviousness > Elements & Tests > General Overview

[HN5] The skepticism of an expert, expressed before inventors proved him wrong, is entitled to fair evidentiary weight.

COUNSEL:

Douglas N. Deline, The Dow Chemical Co., argued for Appellant. With him on the brief was Bernd W. Sandt.

John H. Raubitschek, Associate Solicitor, Office of the Solicitor, argued for Appellee. With him on the brief were Joseph F. Nakamura, Solicitor and Fred E. McKelvey, Deputy Solicitor.

JUDGES:

Smith, Nies, and Newman, Circuit Judges.

OPINIONBY:

NEWMAN

OPINION:

[*470] NEWMAN, Circuit Judge.

Dow Chemical Company appeals the decisions of the United States Patent and Trademark Office Board of Patent Appeals and Interferences, No. 86-3426 (Feb. 25, 1987) and No. 662-81 (Mar. 25, 1986), together rejecting all the claims on reexamination of United States Patent No. *3,919,354* entitled "Impact Resistant Polymers of a Resinous Copolymer of an Alkenyl Aromatic Monomer and an Unsaturated Dicarboxylic Anhydride.". We reverse.

The Rejection

The invention is an impact resistant rubber-based resin having improved resistance to heat distortion. Claim 28, the broadest claim on appeal, is illustrative:

> 28. A polymer suitable for molding and extrusion, of substantially [**2] improved resistance to mechanical shock and impact, the polymer consisting essentially of the polymerization product of
>
> a. a monovinyl alkenyl aromatic monomer containing up to 12 carbon atoms and having the alkenyl group attached directly to the benzene nucleus, the alkenyl aromatic compound being present in a proportion of from about 65 to 95 parts by weight and from 35 to 5 parts by weight of an unsaturated dicarboxylic acid anhyride readily copolymerizable therewith, and
>
> b. from 5 to 35 parts by weight of a diene rubber per 100 parts of (a) plus (b), the rubber consisting essentially of 65 to 100 weight percent butadiene, or isoprene and up to 35 weight percent of an alkenyl aromatic hydrocarbon as the sole other monomer in the rubber, the rubber having a glass temperature not higher than 0 degrees C., the rubber being in the form of a plurality of particles having diameters within the range of 0.02 to 30 microns dispersed throughout a matrix of polymer of alkenyl aromatic monomer and the anhydride, at least a major portion of the rubber particles containing distinct occlusions of the polymer of (a), with the further limitation that
>
> the polymer of (a) is a nonequimolar [**3] random copolymer.

[*471] The preferred ingredients are styrene, maleic anhydride, and synthetic diene rubbers, and our discussion will be in these terms, as was the Board's.

The Board's decision that the claimed invention would have been obvious in terms of *35 U.S.C. § 103* was based on the combination of two references: a 1966 article by Molau and Keskkula entitled "Heterogeneous Polymer Systems IV. Mechanism of Rubber Particle Formation in Rubber-Modified Vinyl Polymers", and Baer U.S. Patent No. *2,971,939*. Also discussed were Farmer U.S. Patent No. *2,275,951* and a publication by Bacon and Farmer entitled "The Interaction of Maleic Anhydride with Rubber", although the Board stated that the rejection was sustainable without relying on either of these references.

The Prior Art

The Molau/Keskkula article shows the preparation of a resin having high impact strength by dissolving synthetic diene rubber in styrene and polymerizing the

styrene. This reference teaches that phase inversion is necessary to the formation of these moldable, extrudable resins. Baer prepares nonequimolar random maleic anhydride-styrene copolymers by a technique [**4] whose salient feature is adding the maleic anhydride slowly to polymerizing styrene under controlled conditions.

Farmer shows the reaction among natural rubber, styrene, and maleic anhydride, and also states that maleic anhydride reacts directly with the rubber. The Bacon and Farmer article also shows the reaction of maleic anhydride with natural rubber. These products, according to Dow's evidence and as found by the Board, do not have a dispersed rubber phase containing occlusions, and are not moldable.

Dow argues that the Board has engaged in hindsight reconstruction of the claimed invention. To support its position Dow refers to several scientific publications and other references, in addition to those cited by the PTO, and evidence submitted by declaration and deposition.

The first group of references to which Dow refers shows the reaction of maleic anhydride with natural or synthetic rubbers. These references show both intermolecular and intramolecular reactions between maleic anhydride and the various rubbers, but not a grafted rubber, which is said by Dow to characterize its product. Additional references are cited by Dow to show that maleic anhydride is much more reactive [**5] with diene-type synthetic rubbers than with natural rubber, and that the reaction with the synthetic rubbers is difficult to control and the product is unpredictable.

Another reference cited by Dow, the *Encyclopedia of Science and Technology*, states the general rule, derived from experience with acrylonitrile, that copolymers with synthetic diene rubbers have elevated glass transition temperatures; Dow advises that this is a highly undesirable property for a high-impact strength resin.

Another series of references cited by Dow shows several known techniques of reacting styrene and maleic anhydride to prepare nonequimolar copolymers, all different from the technique shown in the Baer patent.

Analysis

The Board held that the claimed product results from the application of the Baer technique to a styrene-maleic anhydride polymer system which includes synthetic diene rubber, and that it would have been obvious to do that which these inventors did if one wanted to increase the heat stability of a known high impact styrene rubber resin.

The crux of Dow's argument is that no reference shows or suggests that these references should or could be combined successfully. Indeed, [**6] the Board agreed, stating that "it is not apparent from the evidence whether rubber and maleic anhydride would have been expected to react *in the process suggested by the combined disclosure of Molau and Baer* . . . ." (Emphasis in original).

Dow also points out, referring to the Keskkula evidence, that it was believed that these products could not be made by [*472] the mass polymerization techniques of the prior art. Dow asserts that no reference, including Baer, suggested that the Baer technique could produce the requisite phase inversion in a system containing diene rubber, and could produce a diene-rubber containing resin that could be molded and had the other desired high-impact and thermal properties.

Dow refers to the Farmer patent, cited by the examiner and the Board, which shows that the reaction of styrene, maleic anhydride, and natural rubber forms a product that is unsuitable as a molding resin. Dow argues that Farmer leads away from the Dow invention, in that Farmer obtains precisely the "runaway" reaction, and undesirable product, that Keskkula believed was characteristic of reactions involving styrene, maleic anhydride, and rubbers. Dow points to Dr. Keskkula's [**7] Report to Dow management, written in 1966 at about the time the present invention was made, pointing out the many problems in attempting to produce the three-component product that these inventors later succeeded in producing.

In response, the Commissioner argues that even though an expert polymer scientist, Dr. Keskkula, "personally may have been surprised by the invention at the time it was made, it does not necessarily follow that the invention would have been unobvious to one of ordinary skill in the art." The Commissioner suggests that one less encumbered by knowledge of the need for phase inversion, as described in the Molau/Keskkula article, might have achieved the Dow product by combining the references in the way suggested by the Commissioner. Reflecting on this theory of invention, we observe that such a person did not do so, despite the decades of experimentation with these components, and the recognition of need, as evidenced by the many references cited by both sides. *See In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).* [**8]

The Board held that Dow's statement in the patent specification that it was known that styrene/maleic anhydride copolymers had improved heat resistance as compared with styrene rubbers, made it prima facie

obvious to combine these three components. Indeed, the record shows that such combinations had previously been made, in various ways, but without producing the product here desired. That there were other attempts, and various combinations and procedures tried in the past, does not render obvious the later successful one. The PTO's reliance on Dow's "admission" of longfelt need as prima facie evidence of obviousness is contrary to logic as well as law. [HN1] Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness. *Graham v. John Deere Co., 383 U.S. 1, 17, 148 USPQ 459, 467, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966); Custom Accessories v. Jeffrey-Allan Industries, 807 F.2d 955, 960, 1 USPQ2d 1196, 1199 (Fed. Cir. 1986).* Further, a patent applicant's statement of the purpose of the work is not prior [**9] art.

The Board thus concluded that although one would not know in advance whether the Baer technique would work at all in the presence of diene rubber, or produce a moldable high-impact product, if it did succeed it would have been obvious. The Board criticized Keskkula's evidence for not stating whether, after these inventors proposed the procedure here at issue, Keskkula would have expected the maleic anhydride to react preferentially with the diene rubber or with the styrene and to what effect on the impact properties of the product. The PTO argues that unless the prior art is shown to have led one of ordinary skill to expect the Baer technique to fail, the applicant's burden is not met. This is not the criterion. That these inventors eventually succeeded when they and others had failed does not mean that they or their colleagues must have expected each new idea to fail. Most technological advance is the fruit of methodical, persistent investigation, as is recognized in *35 U.S.C. § 103* [HN2] ("Patentability shall not be negatived by the manner in which the invention was made").

[*473] [**10] [HN3] The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. *See Burlington Industries v. Quigg, 822 F.2d 1581, 1583, 3 USPQ2d 1436, 1438 (Fed. Cir. 1987); In re Hedges, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986); Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 1013, 217 USPQ 193, 200 (Fed. Cir. 1983); In re Rinehart, 531 F.2d 1048, 1053-54, 189 USPQ 143, 148 (CCPA 1976).* Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.

[HN4] In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention. The [**11] Commissioner argues that since the PTO is no longer relying on Farmer or the Bacon and Farmer article, the applicant is creating a "straw man". It is indeed pertinent that these references teach against the present invention. Evidence that supports, rather than negates, patentability must be fairly considered.

The PTO presents, in essence, an "obvious to experiment" standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure. *Interconnect Planning Corporation v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985).* Of the many scientific publications cited by both Dow and the PTO, none suggests that any process could be used successfully in this three-component system, to produce this product having the desired properties. [HN5] The skepticism of an expert, expressed before these inventors proved him wrong, is entitled to fair [**12] evidentiary weight, *see In re Piasecki, 745 F.2d 1468, 1475, 223 USPQ 785, 790 (Fed. Cir. 1984); In re Zeidler, 682 F.2d 961, 966, 215 USPQ 490, 494 (CCPA 1982),* as are the five to six years of research that preceded the claimed invention. The evidence as a whole does not support the PTO's conclusion that the claimed invention would have been obvious in terms of *35 U.S.C. § 103.*

REVERSED.

LEXSEE 119 F3RD 953

ARKIE LURES, INC., Plaintiff-Appellee, v. GENE LAREW TACKLE, INC., Defendant-Counterplaintiff/Appellant, v. BOB D. CARNES, Counterdefendant-Appellee.

96-1239

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

119 F.3d 953; 1997 U.S. App. LEXIS 16772; 43 U.S.P.Q.2D (BNA) 1294

July 8, 1997, Decided

SUBSEQUENT HISTORY: [**1] Rehearing Denied and Suggestion for Rehearing In Banc Declined September 11, 1997, Reported at: *1997 U.S. App. LEXIS 27172.*

PRIOR HISTORY: Appealed from: U.S. District Court for the Western District of Arkansas.

DISPOSITION: REVERSED AND REMANDED

CASE SUMMARY:

PROCEDURAL POSTURE: Appellant inventor sought review of a decision by the United States District Court for the Western District of Arkansas, which granted summary judgment in favor of appellee copier in the copier's declaratory judgment action against the inventor on grounds that the inventor's patent was nonobvious and thus invalid.

OVERVIEW: The inventor combined the idea of a salt base with a plastic lure to create a salt-impregnated plastic lure, which he had patented. A copier subsequently replicated the inventor's combination and declined the inventor's offer for a license. The copier contended that the inventor's salty plastic lure was "not sufficiently different" from the prior art as to render it nonobvious. The court held that the inventor's salty plastic lure was nonobvious, after making an inquiry into the (1) scope and content of the prior art; (2) differences between the prior art and the claimed invention; (3) the level of ordinary skill in the field of invention; and (4) any objective indicia such as commercial success, long felt need, and copying. The court found that no prior art showed or suggested the combination of a plastic lure with salt, and that experts had cautioned the inventor against the combination. The court held that the fact that the combination was not viewed as technically feasible was evidence of nonobviousness.

OUTCOME: The court reversed summary judgment in favor of the inventor and remanded for further proceedings.

CORE TERMS: lure, salt, plastic, plastisol, fish, patent, invention, salty, fishing, attractant, taste, obviousness, organic, bait, body part, summary judgment, skill, odor, additive, texture, hook, secondary, discloses, rind, pork, solvent, surface, impregnated, conventional, manufacturing

LexisNexis(R) Headnotes

Civil Procedure > Appeals > Standards of Review > De Novo Review
Civil Procedure > Summary Judgment > Burdens of Production & Proof
Civil Procedure > Summary Judgment > Summary Judgment Standard
[HN1] An issue may be decided by summary judgment when no material question of fact is in dispute, or when it is shown that the nonmovant can not prevail even on its version of the facts, thus rendering a trial futile. The party moving for summary judgment bears the initial burden of coming forward with evidence that demonstrates the absence of a genuine material question of disputed fact and establishes that the moving party is entitled to judgment as a matter of law. When the movant

has met this initial burden the non-movant must come forward with sufficient evidence to show that, on the non-movant's evidence, the movant is not entitled to judgment as a matter of law. The court reviews de novo a grant of summary judgment.

Patent Law > Claims & Specifications > Enablement Requirement > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN2] The Supreme Court has held that in determining obviousness under *35 U.S.C.S. § 103,* four kinds of factual inquiries are conducted: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the field of the invention; and (4) any objective indicia such as commercial success, long felt need, and copying.

Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN3] The decision of obviousness vel non is made not from the viewpoint of the inventor, but from the viewpoint of a person of ordinary skill in the field of the invention.

Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN4] The public and commercial response to an invention is a factor to be considered in determining obviousness, and is entitled to fair weight.

Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN5] The considerations of commercial success, licensing activity, and copying, may be highly probative of the issue of nonobviousness.

Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN6] Evidence that the combination was not viewed as technically feasible must be considered, for conventional wisdom that a combination should not be made is evidence of nonobviousness.

COUNSEL: Boyd D. Cox, of Fayetteville, Arkansas, argued for plaintiff-appellee and counterdefendant-appellee. With him on the brief was Michael H. Mashburn, Mashburn & Taylor, of Fayetteville, Arkansas. Of counsel on the brief was Bill Putman, Jr., Mashburn & Taylor, of Fayetteville, Arkansas.

Gary Peterson, Pray, Walker, Jackman, Williamson & Marlar, of Oklahoma City, Oklahoma, argued for defendant-counterplaintiff/appellant.

JUDGES: Before ARCHER, Chief Judge, NEWMAN and MICHEL, Circuit Judges. Opinion for the court filed by Circuit Judge Newman. Dissenting opinion filed by Circuit Judge Michel.

OPINIONBY: NEWMAN

OPINION: [*954] NEWMAN, Circuit Judge.

Gene Larew Tackle, Inc. (herein Larew) appeals the summary judgment of the United States District Court for the Western District of Arkansas, n1 declaring invalid United States Patent No. *4,530,179* (the *'179* or Larew patent) entitled "Salt Impregnated Fishing Lure." We reverse the judgment of invalidity and remand for determination of the remaining issues.

N1 *Arkie Lures, Inc. v. Gene Larew Tackle, Inc. v. Bob D. Carnes, 912 F. Supp. 422, 38 U.S.P.Q.2D (BNA) 1300 (W.D. Ark. 1996).*

[**2]

BACKGROUND

Gene Larew, a retired engineer, set out to make a plastisol fishing lure that would have a salty taste for a prolonged period in water, as compared with the salty baits then known. It is explained in the Larew patent that a striking fish will retain a salty-tasting lure for a longer time, thereby improving the fisherman's chance to set the hook.

Mr. Larew's attempts to develop and manufacture a plastic salty lure encountered great skepticism within the fishing lure trade. Although he had made samples by hand he was rebuffed by manufacturers of plastic lures, who expressed strong doubts [*955] about the feasibility of manufacturing such a device, as well as doubts about its properties if it could be made. Two such manufacturers testified on Larew's behalf in response to Arkie Lures' motion for summary judgment. They explained that salt is an undesirable additive for a plastic lure because it tends to roughen the smooth texture of the surface of the lure; that the presence of salt reduces the tensile strength of the plastic, rendering the lure susceptible to tearing and interfering with its flexibility; and that it is unsafe to mix chemicals such as salt with plastic, because [**3] such mixing can cause violent explosions.

Upon extreme persistence by Mr. Larew the product was eventually produced. The first commercial salt-impregnated plastic lure was called the "Gene Larew Salty Frog." It was an immediate commercial success. Arkie Lures copied the Larew lure and, declining Mr. Larew's offer of a license, brought this declaratory

judgment action. The district court granted Arkie Lures' motion for summary judgment of invalidity, concluding that Larew's invention was "not sufficiently different" from the prior art as to render it nonobvious. This appeal followed.

DISCUSSION

A. Standard of Review

[HN1]

An issue may be decided by summary judgment when no material question of fact is in dispute, *Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 251-52, 91 L. Ed. 2d 202, 106 S. Ct. 2505 (1986),* or when it is shown that the nonmovant can not prevail even on its version of the facts, thus rendering a trial futile. *Matsushita Elec. Industrial Co. v. Zenith Radio Corp., 475 U.S. 574, 587, 89 L. Ed. 2d 538, 106 S. Ct. 1348 (1986); Allied Colloids, Inc. v. American Cyanamid Co., 64 F.3d 1570, 1573, 35 U.S.P.Q.2D (BNA) 1840, 1841 (Fed. Cir. 1995).* The party moving for summary judgment bears the initial burden of coming forward with evidence that demonstrates [**4] the absence of a genuine material question of disputed fact and establishes that the moving party is entitled to judgment as a matter of law. *Celotex Corp. v. Catrett, 477 U.S. 317, 323, 91 L. Ed. 2d 265, 106 S. Ct. 2548 (1986).* When the movant has met this initial burden the non-movant must come forward with sufficient evidence to show that, on the non-movant's evidence, the movant is not entitled to judgment as a matter of law. *Id. 477 U.S. 317 at 322-24.* We review de novo the district court's grant of summary judgment. *Celotex, 477 U.S. at 323; Seal-Flex, Inc. v. Athletic Track and Court Construction, 98 F.3d 1318, 40 U.S.P.Q.2D (BNA) 1450 (Fed. Cir. 1996).*

B. The Obviousness Criteria

[HN2]

The Supreme Court in *Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 U.S.P.Q. (BNA) 459, 467, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966)* explained that in determining obviousness under *35 U.S.C. § 103* four kinds of factual inquiries are conducted: the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the field of the invention, and any objective indicia such as commercial success, long felt need, and copying. In *Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 872, 228 U.S.P.Q. (BNA) 90, 98 (Fed. Cir. 1985)* the Federal Circuit [**5] elaborated:

> In patent cases, the need for express Graham findings takes on an especially significant role because of an occasional tendency of district courts to depart from the Graham test, and from the statutory standard of obviousness that it helps determine, to the tempting but forbidden zone of hindsight.

Larew states that the district court failed to consider all of the Graham factors, improperly found facts on summary judgment, and erred in its conclusion. Arkie Lures responds that there was no genuine dispute as to any of the Graham factors, but only a dispute as to the legal conclusion of obviousness. We review the subject matter before the district court in order to ascertain whether summary disposition was available and, if so, whether it was correctly granted.

1. Scope and Content of the Prior Art

The district court determined, and we agree, that there was no dispute as to the scope and content of the prior art. The use [*956] of salty bait to catch fish was known, plastisol lures were known, and the prior art showed the use of organic fish attractants in plastic lures (while cautioning against insoluble attractants). No reference showed or suggested a plastisol salty lure. [**6]

Included in the prior art was a 1972 article entitled "Spice Up Your Lures," which stated that fish "taste" the lure before biting. The Modern Book of the Black Bass, published in 1972, described the use of salted pork rind as bait. United States Patent No. *3,079,722* to Greenlee described a fishing fly formed from squirrel hair with yeast and salt baked in, and explained that salt is an attractant to fish. United States Patent No. *2,979,778* to FitzSimons described a plastic lure containing an organic fish attractant, preferably rhodinyl acetate; this reference warned against the use of insoluble additives in plastic lures. A patent to Orn suggested as lure additives fish attractants having "the flavor or odor of natural bait." The record states that frozen salted minnows have been used to catch trout. The literature on fishing lures is apparently quite extensive, but despite the long use of salty lures and plastic lures, no reference was cited that showed or suggested this combination.

2. Differences Between the Prior Art and the Claimed Invention

Larew stressed four principal differences from the prior art: 1) the Larew lure works not by odor, like the attractant-carrying lures [**7] of the FitzSimons and other references, but because of its salty taste whereby it is mouthed by a striking fish for a longer period of time, thereby increasing the chance to hook the fish before it rejects the bait; 2) the salt-impregnated plastisol retains its salty taste for the life of the lure and does not spoil, unlike known salty baits such as pork rind, which lose their salt in water and rot in storage; 3) manufacture of the salt-impregnated plastisol was widely thought to be unfeasible or unsafe, and the prior art warned against the

addition of solid additives; and 4) the salt was expected to roughen the surface of the plastic as well as change its texture, making it susceptible to tearing and also reducing the action of the lure.

There was no material dispute as to the nature of the differences between the prior art and the claims of the *'179* patent. n2 Although the evidence was not free of argument, it was not disputed that no prior art reference showed a plastic salty lure, and that the differences that are reported are factually correct.

n2 Claim 1 is the broadest claim:

> **1.** In a fishing lure comprising a body part and at least one hook part connected thereto, the improvement wherein said body part is formed of a plastisol of a resin dispersed in an organic solvent, said plastisol being impregnated with sufficient salt to impart a salty taste to said body part.
>
> Other claims are specific to the use of a vinyl chloride resin, a diester plasticizer, and various concentration limitations including the presence of salt in the amount of about one pound per 5-20 gallons of plastisol. Larew objects that the district court did not distinguish among the claims.

[**8]

3. Level of Ordinary Skill in the Field of the Invention

[HN3] The decision of obviousness vel non is made not from the viewpoint of the inventor, but from the viewpoint of a person of ordinary skill in the field of the invention. *Kloster Speedsteel AB v. Crucible, Inc., 793 F.2d 1565, 1574, 230 U.S.P.Q. (BNA) 81, 86 (Fed. Cir. 1986);* see generally *Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 697, 218 U.S.P.Q. (BNA) 865, 868-69 (Fed. Cir. 1983)* (identifying criteria relevant to determination of the level of ordinary skill). The purpose is to assure an appropriate perspective of the decisionmaker, and to focus on conditions as they existed when the invention was made. Good ideas may well appear "obvious" after they have been disclosed, despite having been previously unrecognized.

Larew submitted the affidavit testimony of two persons skilled in the manufacture of plastic lures, Glen Carver and Hugh Harville. Carver was described by the district court as having "an M.S. in biology and chemistry and a Ph.D. in biology and was the head of the biology department at McNeese State." In the 1970s Dr. Carver was a consultant to the fishing tackle industry and helped develop the injection-molding process [**9] that is the [*957] dominant process for producing soft-bodied plastisol fishing lures. Despite Carver's high level of skill, he described his extreme skepticism of the feasibility of Larew's idea, and his belief that a satisfactory product could not be produced.

Mr. Harville was a custom manufacturer of soft-bodied plastic fishing lures. He described his concerns for manufacturing safety, his skepticism as to feasibility, and his expectation that the surface would be roughened and weakened, destroying the lure's efficacy. He described the extraordinary precautions he took upon first attempting to combine the ingredients in accordance with Mr. Larew's formulations.

The evidence showed the complexity of the plastic fishing lure art. Those in the field of the invention viewed Larew's invention not as a simple concept of adding salty taste to a known lure, but as a complex combination requiring experience of fishing and fishing lures and the technology of plastics.

4. Objective Indicia

In Graham the Supreme Court explained that [HN4] the public and commercial response to an invention is a factor to be considered in determining obviousness, and is entitled to fair weight. *383 U.S. at 35-36, 148* [**10] *U.S.P.Q. at 474.* The so-called "secondary considerations" provide evidence of how the patented device is viewed by the interested public: not the inventor, but persons concerned with the product in the objective arena of the marketplace. In this case [HN5] the considerations of commercial success, licensing activity, and copying were markedly prevalent, and were not disputed. Such aspects may be highly probative of the issue of nonobviousness. This court wrote in *Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-39, 218 U.S.P.Q. (BNA) 871, 879 (Fed. Cir. 1983):*

Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

Larew presented evidence of the rapid growth of its business and the numerous licenses granted. Dr. Carver and Mr. Harville testified that Larew's lure "revolutionized" the industry. Ready recognition of the merits of a new product does not establish obviousness. Commercial success and copying are [**11] tributes to ingenuity, not evidence of legal obviousness. This rule is no less worthy when the new product narrowly fits into a field already well explored -- like the fishing lure art --

than when a transcendent scientific breakthrough is launched. The patent law is designed to serve the small inventor as well as the giant research organization.

C. The Obviousness Determination We apply the law of obviousness to the undisputed Graham factors.

No prior art showed or suggested the combination of a plastisol lure with salt, although the prior art was extensive as to the separate elements, and suggested including organic attractants in plastic lures. Instead, the prior art, and the experts, counselled against the Larew combination. The references before the district court, such as the Modern Book of the Black Bass, suggest using salted pork rind or other salty baits, not the incorporation of salt into a plastisol. And FitzSimons, who shows the addition of organic attractants to the plastisol lure, strongly cautions against the addition of plastic-insoluble additives.

The question is not whether salt "could be used," as the district court concluded, but whether it was obvious to [**12] do so in light of all the relevant factors. The beliefs of those in the field at the time, including beliefs that the plastisol lure would lose its surface qualities, texture, and strength, as well as the manufacturing uncertainties, are the position from which the decisionmaker must view the invention.

It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements. Indeed, the years [*958] of use of salty bait and of plastic lures, without combining their properties, weighs on the side of unobviousness of the combination. Mr. Larew persisted against the accepted wisdom, and succeeded. [HN6] The evidence that the combination was not viewed as technically feasible must be considered, for conventional wisdom that a combination should not be made is evidence of unobviousness. See *In re Hedges, 783 F.2d 1038, 1041, 228 U.S.P.Q. (BNA) 685, 687 (Fed. Cir. 1986)* (proceeding against accepted wisdom is evidence of unobviousness). Whether some plastics manufacturers knew how to mix salt and plastisol, as was argued to the district court, did not make it obvious to proceed against the general [**13] view in the field of plastic fish lures. FitzSimons' warning against adding plastic-insoluble ingredients to the plastisol was repeated by Dr. Carver and Mr. Harville, and Mr. Larew was so advised long before this litigation arose. Further, these artisans of the plastic lure believed that salt would affect the surface, texture, and strength of the lure. Larew's eventual demonstration that the desired product could indeed be successfully made did not render it obvious, nor did the ready appreciation of its value render it unpatentable.

The district court's statement that "secondary considerations are just that -- secondary," suggests a misperception of the role of these considerations in determination of the ultimate question. The record shows the strong commercial recognition of this seemingly simple invention. Although the district court concluded that "The fact that Larew was the first to try this obvious possibility and found that there is more consumer demand than one might think does not mean he was being inventive," this invokes an incorrect standard. On the correct standard, we look to the state of relevant knowledge at the time of Larew's activities, including concern for [**14] the quality of the product, the warnings, and the perceived manufacturing difficulties, all manifested in the widespread skepticism that Mr. Larew encountered among those of skill in the field.

The conclusion of obviousness was in error, and is reversed. The case is remanded to the district court for further proceedings.

Costs to Larew.

REVERSED AND REMANDED

DISSENTBY: MICHEL

DISSENT: MICHEL, Circuit Judge, dissenting.

I respectfully dissent. The district court correctly held, in a thorough and well-reasoned opinion, that United States Patent No. *4,530,179* ("the *'179* patent"), issued in 1985, was invalid because the fishing lure it claims would have been obvious under *35 U.S.C. § 103* in light of the prior art before the district court. I would not overturn that decision and do not believe the majority has shown a basis for doing so.

The *'179* patent has 20 claims. Only three of the claims -- 1, 11, and 20 -- are independent. Claim 1 reads as follows:

In a fishing lure comprising a body part and at least one hook part connected thereto, the improvement wherein said body part is formed of a plastisol of a resin dispersed in an organic solvent, said plastisol being impregnated [**15] with sufficient salt to impart a salty taste to said body part.

Claim 11 reads as follows:

A body for a fishing lure in the form of a soft-bodied animal, said body being formed of a plastisol of a resin dispersed in an organic solvent, said plastisol being impregnated with sufficient salt to impart a salty taste to said body part.

Claim 20 reads as follows:

A body for a fishing lure in the form of a soft-bodied worm, frog or lizard, said body being formed of a resilient plastic material impregnated with sufficient salt to impart a salty taste to said body part, said plastic material being substantially free of organic fish attractant.

The dependent claims contain additional limitations, concerning, for example, the shape of the lure, the type of plastisol, and the amount of salt.

The *'179* patent itself admits that all of the elements of the claimed invention, other than the addition of salt to a conventional plastisol lure, were known in the art. For example, the patent specification states the following:

Conventional fishing lures having soft plastic bodies are well known. Such lures are [*959] frequently formed as worms, frogs, lizards, small fish or the [**16] like. In addition to the body part, such lures include a hook part, comprising one or more hooks, and an attachment part for attaching the lure to the line. . . . In some instances, such lures include an oderant which produces a scent to attract fish.

Col. 1, ll. 8-22.

The plastisol is formulated and heated according to known techniques for controlling the properties of plastisols, to give the lure body a desired degree of resilience and tensile strength.

Col. 2, ll. 3-6.

With respect to the limitation of claim 20 regarding the absence of "organic fish attractant," the "Background of the Invention" section of the *'179* patent recognizes this limitation was present in the prior art. There, the patentee discussed the use of conventional plastic lures that attract fish due to their physical resemblance to frogs, insects or other animals, their "flash" as they move through the water and the sound waves they create. Col.1, ll. 8-22. The patentee also disclosed that, "in some instances," odorants could be added. Col. 1, ll. 21-22. It is inferable that at least the conventional lures without odorants did not contain organic attractants. With respect to the limitation regarding [**17] the use of an organic solvent to disperse the plastic, the patent discloses that "many different plasticizers may be used in the plastisols, and may be chosen in accordance with known criteria to provide proper physical properties . . . ." Col. 2, ll. 20-25. Moreover, one of the solvents explicitly disclosed by Larew is also disclosed by the prior art, United States Patent No. *2,979,778* to FitzSimons ("the *'778* patent").

Therefore, the only new element is the addition of salt as a non-organic attractant. However, it is beyond dispute that it was known in the prior art that fish are attracted to certain smells and tastes. As discussed by the district court, the *'778* patent clearly discloses that fish are attracted to certain tastes. An object of the invention of the *'778* patent was to "provide a method for making an artificial lure having an odor and texture that duplicates, as nearly as possible, the odor and texture or taste of natural bait." In hypothesizing why the invention was successful, the *'778* patent states that the fish appeared to not be discouraged by one unsuccessful nibble but instead returned in an effort to consume the entire bait, likely "attributable to the fact [**18] that the texture of the plastic body simulates the taste of the nymph, while the attractant simulates its odor." Likewise a 1972 article states that fish depend heavily on their senses of smell and taste. Richard Martin, "Spice Up Your Lures," Outdoor Life, December 1972 at 80. This article also discloses that one study showed that certain fish are "able to detect salt and sugar in truly miniscule amounts." Id. at 127. Although not discussed by the district court, United States Patent No. *3,854,234*, cited in the *'179* patent, discloses an artificial bait with a doughball-type core incorporating cheese, animal by-products, corn syrup or cereal grain which "emits enticing and tantalizing odors and a flavor source known to be savory and attractive to fish."

Moreover, the prior art demonstrates that the particular substance used as a flavor source in this invention -- salt -- was a known fish attractant. For example, in Byron Dalrymple, Modern Book of the Black Bass 90 (1972), the author states:

Salt is definitely an attractor. This is thought to be the reason that solutions used to preserve such items as pork rind, which contain much salt, are actually an attractor. I have caught [**19] dozens of bass with fly-fishing tackle using a small strip of pork rind taken from a salt solution and impaled on a bare hook. I have watched many of them take the lure. They approach, appear to sniff or evaluate it, then inhale it.

Also, United States Patent No. *3,079,722*, issued in 1963, discloses a fishing lure with an inner body portion consisting of water, yeast, salt and squirrel hair. When the inner body becomes moist, it "emits a peculiar odor which is very effective in attracting fish to the lure." Additionally, an entry entitled the Salted Dynamite for Lunker Trout, in The 1974 Sports Afield Almanac (Ted Kesting ed., 1974) discloses that one method of catching

[*960] bigger fish is to add salt to minnows and freeze before use. The almanac further states "real monster trout will take those salt-flavored minnows as if they are going out of style." Id.

Thus, it was well-known in the art that fish were attracted by certain smells and tastes and that salt was just such an attractor, even in small quantities. In light of this prior art, the district court correctly held that the *'179* patent is invalid for obviousness.

I believe the strongest argument presented by Gene Larew [**20] Tackle, Inc. ("Larew") and the majority opinion in favor of reversing the district court is that the prior art taught away from adding salt to a plastic lure. Larew argues the *'778* patent "specifically cautioned against the use of any plastic-insoluble additive as a fish attractant in his plastisol lure." Larew also points to the testimony of two witnesses who testified that they were afraid a violent reaction, even an explosion, might occur if a foreign substance was added to the plastisol.

This argument, however, does not change my view of the correct outcome. The *'778* patent actually says only that "while a wide variety of attractant materials are available, it is desirable that the oil or other attractant be miscible in the plasticizer." Thus, it does not specifically caution against the use of salt, but only suggests the use of a miscible, i.e., a mixable, material is more desirable. Salt is miscible in plastic, at least long enough to pour the lures, as evidenced by the success of the salty lures. It is not required to be soluble. Thus, the *'778* patent does not teach away from the invention of the *'179* patent.

As for the testimony of the witnesses, which we assume to [**21] be true on summary judgment, such testimony is insufficient to overcome the overwhelming evidence of obviousness before the district court. Those of skill in the art had been adding a variety of substances to plastic lures for quite some time, see, e.g., the *'778* patent, and Larew has failed to point to any evidence which would demonstrate that salt was thought to be any different than any of the other additives. Moreover, the trial court found that the record demonstrated as a matter of law that two other individuals had added some quantity of salt to their lures, either as a filler or to keep the mold from sticking, without ill effect.

Likewise, even when the evidence of secondary indicia of obviousness is considered, as it must be, my view of the correct result is not changed. Even where such evidence exists, it may not be compelling enough to overcome the strong showing of obviousness in light of the prior art. See *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp., 72 F.3d 1577, 1583, 37 U.S.P.Q.2D (BNA) 1314, 1318-19 (Fed. Cir. 1996)* ("Considering the minor differences between the claimed invention and the teachings of [the prior art], the secondary considerations were not sufficiently [**22] compelling."). This is such a case.

LEXSEE 149 F3RD 1350

IN RE DENIS ROUFFET, YANNICK TANGUY and FREDERIC BERTHAULT

97-1492

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

149 F.3d 1350; 1998 U.S. App. LEXIS 16414; 47 U.S.P.Q.2D (BNA) 1453

July 15, 1998, Decided

PRIOR HISTORY: [**1] Appealed from: Patent and Trademark Office Board of Patent Appeals and Interferences. (Serial No. 07/888,791).

DISPOSITION: REVERSED.

CASE SUMMARY:

PROCEDURAL POSTURE: Appellant patent applicants sought review of an order of appellee Patent and Trademark Office Board of Patent Appeals and Interferences, which affirmed a patent examiner's rejection of the patent applicants' application on grounds that it was obvious under *35 U.S.C.S. § 103*(a).

OVERVIEW: The court held that the Patent and Trademark Office Board of Patent Appeals and Interferences (Board) committed reversible error when it determined that there was "motivation" to combine the elements of two prior lines of patents in a manner that rendered the patent applicants' claimed invention obvious under *35 U.S.C.S. § 103*(a). The court held that the Board's naked invocation of "skill in the art" to supply a "suggestion to combine" the previous patents lines of patents cited by the Board was clearly erroneous. The fact that the Board merely observed that the level of skill in the art was very high, and did not identify the specific principle known to one of ordinary skill in the art that would have suggested the claimed combination, led the court to infer that the Board's finding of obviousness improperly relied on hindsight.

OUTCOME: The court reversed the order of the Patent and Trademark Office Board of Patent Appeals and Interferences, which denied the patent applicants' application.

CORE TERMS: satellite, invention, beam, skill, obviousness, combine, handover, orbit, footprint, teach, motivation, examiner, station, teaching, prima facie case, patentability, fan, artisan, transmitted, travel, skilled, patent, high level, plurality, hindsight, alignment, surface, antenna, loop, cell

LexisNexis(R) Headnotes

Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness
Patent Law > Nonobviousness > Evidence & Procedure > Presumptions & Proof
Patent Law > Nonobviousness > Elements & Tests > Secondary Considerations
[HN1] To reject claims in a patent application under *35 U.S.C.S. § 103,* an examiner must show an unrebutted prima facie case of obviousness. In the absence of a proper prima facie case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent. On appeal to the Patent and Trademark Office Board of Patent Appeals and Interferences, an applicant can overcome a rejection by showing insufficient evidence of prima facie obviousness or by rebutting the prima facie case with evidence of secondary indicia of non-obviousness.

Patent Law > U.S. Patent & Trademark Office Proceedings > Appeals
Civil Procedure > Appeals > Standards of Review > Clearly Erroneous Review
Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
[HN2] While this court reviews the Patent and Trademark Office Board of Patent Appeals and

Interferences' (Board) determination in light of the entire record, an applicant may specifically challenge an obviousness rejection by showing that the Board reached an incorrect conclusion of obviousness or that the Board based its obviousness determination on incorrect factual predicates. This court reviews the ultimate determination of obviousness as a question of law. The factual predicates underlying an obviousness determination include the scope and content of the prior art, the differences between the prior art and the claimed invention, and the level of ordinary skill in the art. This court reviews the Board's factual findings for clear error. A finding is clearly erroneous when, although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.

Patent Law > Nonobviousness > Evidence & Procedure > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN3] The secondary considerations are also essential components of the obviousness determination. This objective evidence of non-obviousness includes copying, long felt but unsolved need, failure of others, commercial success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention.

Patent Law > U.S. Patent & Trademark Office Proceedings > Appeals
Civil Procedure > Appeals > Standards of Review > Clearly Erroneous Review
Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness
[HN4] The Patent and Trademark Office Board of Patent Appeals and Interferences (Board) must consider all of the applicant's evidence. An observation by the Board that the examiner made a prima facie case is not improper, as long as the ultimate determination of patentability is made on the entire record. The courts review factual conclusions drawn from this evidence for clear error. Whether the evidence presented suffices to rebut the prima facie case is part of the ultimate conclusion of obviousness and is therefore a question of law.

Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Nonobviousness > Elements & Tests > Claimed Invention as a Whole
Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > General Overview
[HN5] When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. Although the suggestion to combine references may flow from the nature of the problem, the suggestion more often comes from the teachings of the pertinent references, or from the ordinary knowledge of those skilled in the art that certain references are of special importance in a particular field. Therefore, when determining the patentability of a claimed invention which combines two known elements, the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > General Overview
[HN6] Obviousness is determined from the vantage point of a hypothetical person having ordinary skill in the art to which the patent pertains. This legal construct is akin to the "reasonable person" used as a reference in negligence determinations. The legal construct also presumes that all prior art references in the field of the invention are available to this hypothetical skilled artisan.

Patent Law > Nonobviousness > Evidence & Procedure > Presumptions & Proof
Patent Law > Nonobviousness > Elements & Tests > Hindsight
Patent Law > Nonobviousness > Elements & Tests > Prior Art
[HN7] To prevent the use of hindsight based on the invention to defeat patentability of the invention, the courts require the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

Patent Law > U.S. Patent & Trademark Office Proceedings > Appeals
Patent Law > Nonobviousness > Elements & Tests > Hindsight
Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness
[HN8] Where the Patent and Trademark Office Board of Patent Appeals and Interferences does not explain the

specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of a patent applicant's invention to make the combination, the courts infer that the examiner selected the references with the assistance of hindsight. The courts forbid the use of hindsight in the selection of references that comprise the case of obviousness.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard
Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Nonobviousness > Evidence & Procedure > General Overview
[HN9] The suggestion to combine requirement is a safeguard against the use of hindsight combinations to negate patentability. While the skill level is a component of the inquiry for a suggestion to combine, a lofty level of skill alone does not suffice to supply a motivation to combine. Otherwise a high level of ordinary skill in an art field would almost always preclude patentable inventions. As the courts recognize, invention itself is the process of combining prior art in a non-obvious manner. Therefore, even when the level of skill in the art is high, the Patent and Trademark Office Board of Patent Appeals and Interferences (Board) must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination. In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious.

COUNSEL: Richard C. Turner and Grant K. Rowan, Sughrue, Mion, Zinn, Macpeak & Seas, PLLC, of Washington, DC, argued for appellants.

David J. Ball, Jr., Associate Solicitor, Office of the Solicitor, Patent and Trademark Office, of Arlington, Virginia, argued for appellee. With him on the brief were Nancy J. Linck, Solicitor, Albin F. Drost, Deputy Solicitor, and Craig R. Kaufman, Associate Solicitor. Of counsel was Scott A. Chambers, Associate Solicitor, Office of the Solicitor.

JUDGES: Before PLAGER, Circuit Judge, ARCHER, Senior Circuit Judge, and RADER, Circuit Judge.

OPINIONBY: RADER

[*1352] RADER, Circuit Judge.

Denis Rouffet, Yannick Tanguy, and Frederic Bethault (collectively, Rouffet) submitted application 07/888,791 (the application) on May 27, 1992. The Board of Patent Appeals and Interferences (the Board) affirmed final rejection of the application as obvious under *35 U.S.C. § 103*(a). See Ex parte Rouffet, No. 96-1553 (Bd. Pat. App. & Int. Apr. 16, 1997). Because the Board reversibly erred in identifying a motivation to combine the references, this [**2] court reverses.

I.

Satellites in a geosynchronous or geostationary orbit remain over the same point on the Earth's surface. Their constant position above the Earth's surface facilitates communications. These satellites project a number of beams to the Earth. Each beam transmits to its area of coverage, or footprint, on the Earth's surface. In order to provide complete coverage, adjacent footprints overlap slightly and therefore must use different frequencies to avoid interference. However, two or more non-overlapping footprints can use the same set of frequencies in order to use efficiently the limited radio spectrum. Figure 1 from the application shows the coverage of a portion of the Earth's surface provided by multiple cone shaped beams:

[*1353] [SEE FIGURE 1 IN ORIGINAL]

OPINION:

Frequency reuse techniques, however, have a limited ability to compensate for congestion in geostationary orbits. To alleviate the orbit congestion problem, new telecommunications systems use a network of satellites in low Earth orbit. When viewed from a fixed point on the Earth's surface, such satellites do not remain stationary but move overhead. A satellite's motion as it transmits a plurality of cone-shaped beams [**3] creates a new problem. The satellite's movement causes a receiver on the Earth's surface to move from the footprint of one beam into a second beam transmitted by the same satellite. Eventually, the satellite's motion causes the receiver to move from the footprint of a beam transmitted by one satellite into the footprint of a beam transmitted by a second satellite. Each switch from one footprint to another creates a "handover" event analogous to that which occurs when a traditional cellular phone travels from one cell to another. Handovers are undesirable because they can cause interruptions in signal transmission and reception.

Rouffet's application discloses technology to reduce the number of handovers between beams transmitted by the same satellite. In particular, Rouffet eliminates handovers caused solely by the satellite's motion. To accomplish this goal, Rouffet changes the shape of the beam transmitted by the satellite's antenna. Rouffet's satellites transmit fan-shaped beams. A fan beam has an elliptical footprint. Rouffet aligns the long axis of his beams parallel to the direction of the satellite's motion

across the Earth's surface. By elongating the beam's footprint in the [**4] direction of satellite travel, Rouffet's invention ensures that a fixed point on the Earth's surface likely will remain within a single footprint until it is necessary to switch to another satellite. Because Rouffet's invention does not address handovers caused by the motion of the receiver across the Earth's [*1354] surface. his arrangement reduces, but does not eliminate, handovers. Figure 3 from the application shows the footprints **12** from six beams aligned in the direction of satellite motion **15**:

[SEE FIGURE 3 IN ORIGINAL]

The application contains ten claims that stand or fall as a group. Claim 1 is representative:

> A low orbit satellite communications system for mobile terminals, wherein the communications antenna system of each satellite provides isoflux coverage made up of a plurality of fan beams that are elongate in the travel direction of the satellite.

The examiner initially rejected Rouffet's claims as unpatentable over U.S. Pat. No. *5,199,672* (King) in view of U.S. Pat. No. *4,872,015* (Rosen) and a conference report entitled "A Novel Non-Geostationary Satellite Communications System," Conference Record, International Conference on Communications, [**5] 1981 (Ruddy). On appeal to the Board, the examiner added an alternative ground for rejection, holding that the claims were obvious over U.S. Pat. No. *5,394,561* (Freeburg) in view of U.S. Pat. No. *5,170,485* (Levine).

On April 16, 1997, the Board issued its decision. Because Rouffet had specified that the claims would stand or fall as a group based on the patentability of claim 1, the Board limited its opinion to that claim. The Board unanimously determined that the examiner had properly rejected claim 1 as obvious over King in view of Rosen and Ruddy. The Board, on a split vote, also affirmed the rejection over Freeburg in view of Levine.

[*1355] II

[HN1] To reject claims in an application under section 103, an examiner must show an unrebutted *prima facie* case of obviousness. See *In re Deuel, 51 F.3d 1552, 1557, 34 U.S.P.Q.2D (BNA) 1210, 1214 (Fed. Cir. 1995).* In the absence of a proper *prima facie* case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent. See *In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2D (BNA) 1443, 1444 (Fed. Cir. 1992).* On appeal to the Board, an applicant can overcome a rejection by showing insufficient evidence of *prima* [**6] *facie* obviousness or by rebutting the *prima facie* case with evidence of secondary indicia of nonobviousness. See id.

[HN2] While this court reviews the Board's determination in light of the entire record, an applicant may specifically challenge an obviousness rejection by showing that the Board reached an incorrect conclusion of obviousness or that the Board based its obviousness determination on incorrect factual predicates. This court reviews the ultimate determination of obviousness as a question of law. See *In re Lueders, 111 F.3d 1569, 1571, 42 U.S.P.Q.2D (BNA) 1481, 1482 (Fed. Cir. 1997).* The factual predicates underlying an obviousness determination include the scope and content of the prior art, the differences between the prior art and the claimed invention, and the level of ordinary skill in the art. See *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 881, 45 U.S.P.Q.2D (BNA) 1977, 1981 (Fed. Cir. 1998).* This court reviews the Board's factual findings for clear error. See *In re Zurko, 142 F.3d 1447, 1449, 46 U.S.P.Q.2D (BNA) 1691, 1693 (Fed. Cir. 1998)* (in banc); *Leuders, 111 F.3d at 1571-72.* "'A finding is clearly erroneous when, although there is evidence to support [**7] it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.'" *In re Graves, 69 F.3d 1147, 1151, 36 U.S.P.Q.2D (BNA) 1697, 1700 (Fed. Cir. 1995)* (quoting *United States v. United States Gypsum Co., 333 U.S. 364, 395, 92 L. Ed. 746, 68 S. Ct. 525 (1948)).*

[HN3] The secondary considerations are also essential components of the obviousness determination. See *In re Emert, 124 F.3d 1458, 1462, 44 U.S.P.Q.2D (BNA) 1149, 1153 (Fed. Cir. 1997)* ("Without Emert providing rebuttal evidence, this *prima facie* case of obviousness must stand."). This objective evidence of nonobviousness includes copying, long felt but unsolved need, failure of others, see *Graham v. John Deere Co., 383 U.S. 1, 17-18, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966),* commercial success, see *In re Huang, 100 F.3d 135, 139-40, 40 U.S.P.Q.2D (BNA) 1685, 1689-90 (Fed. Cir. 1996),* unexpected results created by the claimed invention, unexpected properties of the claimed invention, see *In re Mayne, 104 F.3d 1339, 1342, 41 U.S.P.Q.2D (BNA) 1451, 1454 (Fed. Cir. 1997); In re Woodruff, 919 F.2d 1575, 1578, 16 U.S.P.Q.2D (BNA) 1934, 1936-37 (Fed. Cir. 1990),* licenses showing industry respect for [**8] the invention, see *Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 U.S.P.Q.2D (BNA) 1294, 1297 (Fed. Cir. 1997); Pentec, Inc. v. Graphic Controls Corp., 776 F.2d 309, 316, 227 U.S.P.Q. (BNA) 766, 771 (Fed. Cir. 1985),* and skepticism of skilled artisans before the invention, see *In re Dow Chem. Co., 837 F.2d 469, 473, 5 U.S.P.Q.2D (BNA) 1529, 1532 (Fed. Cir. 1988).* [HN4] The Board

must consider all of the applicant's evidence. See *Oetiker, 977 F.2d at 1445* ("An observation by the Board that the examiner made a *prima facie* case is not improper, as long as the ultimate determination of patentability is made on the entire record."); *In re Piasecki, 745 F.2d 1468, 1472, 223 U.S.P.Q. (BNA) 785, 788 (Fed. Cir. 1984).* The court reviews factual conclusions drawn from this evidence for clear error. Whether the evidence presented suffices to rebut the *prima facie* case is part of the ultimate conclusion of obviousness and is therefore a question of law.

[HN5] When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. See *In re Geiger, 815 F.2d 686, 688, 2 U.S.P.Q.2D (BNA) 1276, 1278 (Fed. Cir. 1987).* Although the [**9] suggestion to combine references may flow from the nature of the problem, see *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 U.S.P.Q.2D (BNA) 1626, 1630 (Fed. Cir. 1996),* the suggestion more often comes from the teachings of the pertinent references, see *In re Sernaker, 702 F.2d 989, 994, 217 U.S.P.Q. (BNA) 1, 5 (Fed. Cir. 1983),* or from the ordinary knowledge of those skilled in the art that certain references are of special importance [*1356] in a particular field, see *Pro-Mold, 75 F.3d at 1573* (citing *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297 n.24, 227 U.S.P.Q. (BNA) 657, 667 n.24 (Fed. Cir. 1985)).* Therefore, "when determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" See *In re Beattie, 974 F.2d 1309, 1311-12, 24 U.S.P.Q.2D (BNA) 1040, 1042 (Fed. Cir. 1992)* (quoting *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462, 221 U.S.P.Q. (BNA) 481, 488 (Fed. Cir. 1984)).*

III

The parties agree that the five references asserted by the examiner [**10] are in the same field of endeavor as the invention. The parties also agree that the pertinent level of skill in the art - design of satellite communications systems - is high. On appeal, Rouffet asserts that the examiner and the Board erred by improperly combining references to render the claimed invention obvious.

The Combination of King, Rosen, and Ruddy

The Board first affirmed the rejection of Rouffet's claims over a combination of King, Rosen, and Ruddy. King discloses a system for launching a plurality of satellites into low Earth orbits from a single launch vehicle. Rosen teaches a geostationary satellite that uses a plurality of fan beams with their long axes oriented in an east-west direction to communicate with mobile and fixed terminals on the Earth.

The final, and most important, reference in this combination is Ruddy. Ruddy describes a television broadcast system that uses a series of satellites to retransmit signals sent from a ground station over a wide area. Rather than using a geostationary orbit, Ruddy teaches the use of a series of satellites in Molniya orbits. A satellite in a Molniya orbit always follows the same path through the sky when viewed from a fixed [**11] point on the ground. Viewed from the Earth, the orbital path includes a narrow, elliptical apogee loop. In order to transmit to these moving satellites from a ground station, Ruddy uses a fan beam with a long axis aligned with the long axis of the orbit's apogee loop. This alignment places the entire apogee loop within the footprint of the beam and eliminates the need for the ground station's antenna to track the satellite's motion around the apogee loop. Ruddy further teaches orbit parameters and spacing of multiple satellites to ensure that a satellite is always in the loop to receive and rebroadcast signals from the Earth station.

King and Rosen together teach the use of a network of satellites in low Earth orbit. Thus, Ruddy becomes the piece of the prior art mosaic that shows, in the reading of the Board, the use of "a plurality of fan beams that are elongate in the travel direction of the satellite." Ruddy, however, is different from the claimed invention in several respects. Specifically, the application claims the projection of multiple elliptical fan-shaped footprints from the satellite to the ground. See Claim 1, *supra*, see also Application at 6, lines 9-11 ("In [**12] addition, in this system, the geometrical shape of the beams 12 is changed: instead of being circular they are now elongate ellipses."). The application's written description further teaches that the invention's fan-shaped satellite beams will minimize handovers. See id. at lines 11-16 ("This considerably increases call durations between handovers.").

In contrast, Ruddy teaches that a ground station may use a single fan-shaped beam to transmit to a satellite in a unique Molniya orbit. The ground station transmits a beam into which a series of satellites in Molniya orbits will successively enter. At least two differences are evident: the application teaches projection of multiple beams from a satellite to the Earth, while Ruddy teaches projection of a single beam from the Earth to satellites. Moreover to the extent Ruddy contains a teaching about handovers, its teachings focus on use of the unique Molniya orbit to ensure that a satellite always falls within the beam transmitted by the ground station.

These differences suggest some difficulty in showing a *prima facie* case of obviousness. The Board, however, specifically found that artisans of ordinary skill in this field of [**13] art would know to shift the frame of reference from a ground station following a satellite to a satellite transmitting to the ground. According proper deference to the Board's finding [*1357] of a lofty skill level for ordinary artisans in this field, this court discerns no clear error in the Board's conclusion that these differences would not preclude a finding of obviousness. While Ruddy does not expressly teach alignment of the fan beam with the apparent direction of the satellite's motion, this court perceives no clear error in the Board's determination that Ruddy would suggest such an alignment to one of skill in this art. Therefore, the Board did not err in finding that the combination of King, Rosen, and Ruddy contains all of the elements claimed in Rouffet's application.

However, the Board reversibly erred in determining that one of skill in the art would have been motivated to combine these references in a manner that rendered the claimed invention obvious. Indeed, the Board did not identify any motivation to choose these references for combination. Ruddy does not specifically address handover minimization. To the extent that Ruddy at all addresses handovers due to satellite motion, [**14] it addresses this subject through the selection of orbital parameters. Ruddy does not teach the choice of a particular shape and alignment of the beam projected by the satellite. Thus Ruddy addresses the handover problem with an orbit selection, not a beam shape. The Board provides no reasons that one of ordinary skill in this art, seeking to minimize handovers due to satellite motion, would combine Ruddy with Rosen and King in a manner that would render the claimed invention obvious.

[HN6] Obviousness is determined from the vantage point of a hypothetical person having ordinary skill in the art to which the patent pertains. See *35 U.S.C. § 103*(a). This legal construct is akin to the "reasonable person" used as a reference in negligence determinations. The legal construct also presumes that all prior art references in the field of the invention are available to this hypothetical skilled artisan. See *In re Carlson, 983 F.2d 1032, 1038, 25 U.S.P.Q.2D (BNA) 1207, 1211 (Fed. Cir. 1993).*

As this court has stated, "virtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. (BNA) 865, 870 (Fed. Cir. 1983);* see also [**15] *Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 U.S.P.Q. (BNA) 8, 12 (Fed. Cir. 1983)* ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q.2D (BNA) 1551, 1554 (Fed. Cir. 1996).*

[HN7] To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the [**16] inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

This court has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. In this case, the Board relied upon none of these. Rather, just as it relied on the high level of skill in the art to overcome the differences between the claimed invention and the selected elements in the references, it relied upon the high level of skill in the art to provide the necessary motivation. The Board did not, however, explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the field of art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify [**17] the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness [*1358] construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

[HN8] Because the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of

references that comprise the case of obviousness. See *In re Gorman, 933 F.2d 982, 986, 18 U.S.P.Q.2D (BNA) 1885, 1888 (Fed. Cir. 1991).* Lacking a motivation to combine references, the Board did not show a proper *prima facie* case of obviousness. This court reverses the rejection over the combination of King, Rosen, and Ruddy.

The Combination of Freeburg and Levine

Freeburg teaches a cellular radiotelephone system based on a constellation of low Earth orbit satellites that use conical beams to transmit from [**18] the satellite to both fixed and mobile Earth stations. Levine teaches an Earth-based cellular radio system that uses fan beams broadcast from antenna towers. Levine's elliptical footprints are aligned with the road grid. To increase the capacity of traditional ground-based systems through frequency reuse techniques, Levine teaches the use of antennas that broadcast signals with smaller footprints than the prior art system. Thus, Levine actually increases the number of overlap regions between cells and, hence, the number of potential handovers. Figure 1 of the Levine patent illustrates its alignment of beam footprints:

[SEE FIGURE 1 IN ORIGINAL]

[*1359] As a mobile unit (e.g., a driver using a car phone) moves though a succession of overlapping zones, Levine uses selection algorithms to determine which of the cells is aligned with the travel direction of the mobile unit. These algorithms then select this cell for use while continually monitoring intersecting cells in the event that the mobile unit changes direction.

Once again, this court notes significant differences between the teachings of the application and the Levine-Freeburg combination. The critical Levine reference again involves [**19] a beam from an Earth station without any reference to the "travel direction of [a] satellite." Moreover, Levine actually multiplies the number of potential handovers and then uses software to sort out the necessary handovers from the unnecessary. However, the Board explains the reasons that one possessing the lofty skills characteristic of this field would know to account for the differences between the claimed invention and the prior art combination. This court discerns no clear error in that reliance on the considerable skills in this field.

This court does, however, discern reversible error in the Board's identification of a motivation to combine Levine and Freeburg. In determining that one of skill in the art would have had motivation to combine Levine and Freeburg, the Board noted that "the level of skill in the art is very high." As noted before, this observation alone cannot supply the required suggestion to combine these references. The Board posits that the high level of skill in the art overcomes the absence of any actual suggestion that one could select part of the teachings of Levine for combination with the satellite system disclosed by Freeburg.

As noted above, [HN9] the [**20] suggestion to combine requirement is a safeguard against the use of hindsight combinations to negate patentability. While the skill level is a component of the inquiry for a suggestion to combine, a lofty level of skill alone does not suffice to supply a motivation to combine. Otherwise a high level of ordinary skill in an art field would almost always preclude patentable inventions. As this court has often noted, invention itself is the process of combining prior art in a nonobvious manner. See, e.g., *Richdel, 714 F.2d at 1579; Environmental Designs, 713 F.2d at 698.* Therefore, even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination. Cf. *Gechter v. Davidson, 116 F.3d 1454, 43 U.S.P.Q.2D (BNA) 1030 (Fed. Cir. 1997)* (explaining that the Board's opinion must describe the basis for its decision). In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious.

The Board's naked invocation of skill in the art to supply a suggestion to combine [**21] the references cited in this case is therefore clearly erroneous. Absent any proper motivation to combine part of Levine's teachings with Freeburg's satellite system, the rejection of Rouffet's claim over these references was improper and is reversed.

IV

The Board reversibly erred in determining that there was a motivation to combine either the teachings of King, Rosen, and Ruddy or of Freeburg and Levine in a manner that would render the claimed invention obvious. Because this predicate was missing in each case, the Board did not properly show that these references render the claimed invention obvious. Therefore this court reverses the Board's decision upholding the rejection of Rouffet's claims. In light of this disposition, Rouffet's pending motion to remand the case to the Board for further consideration is denied as moot.

COSTS

Each party shall bear its own costs.

REVERSED.

LEXSEE 947 F2ND 488

IN RE MARK A. VAECK, WIPA CHUNGJATUPORNCHAI and LEE MCINTOSH

No. 91-1120

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

947 F.2d 488; 1991 U.S. App. LEXIS 24846; 20 U.S.P.Q.2D (BNA) 1438

October 21, 1991, Decided

PRIOR HISTORY: [**1] Appealed from: United States Patent and Trademark Office Board of Patent Appeals and Interferences.

DISPOSITION:

Affirmed in Part, Reversed in Part.

CASE SUMMARY:

PROCEDURAL POSTURE: Appellant inventors sought review of a decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences, which rejected their claims as unpatentable under *35 U.S.C.S. § 103* and *35 U.S.C.S. § 112* because their invention was prima facie obvious and disclosure was not enabling.

OVERVIEW: The inventors sought review of the rejection of their patent claims under *35 U.S.C.S. § 103* and *35 U.S.C.S. § 112,* as prima facie obvious, and not enabling, in their application for a genetic engineering technique for the production of insecticidal proteins. The Board of Patent Appeals applied eleven prior art references against the claims. The court reversed the rejection based on obviousness for failure to a establish prima facie case because prior art offered no suggestion of substitution that was different between the claimed invention and prior art and a reasonable expectation of success was not present. The court affirmed the rejection based on enablement, holding that there was no reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought because the disclosure did not enable one of ordinary skill to make and use the invention as recited in the claims without undue experimentation.

OUTCOME: The rejection of the inventors' claims for obviousness was reversed because suggestion and reasonable expectation of success was not present in the prior art. The rejection based on enablement was affirmed because disclosure did not enable one of ordinary skill to make and use the invention without undue experimentation.

CORE TERMS: gene, cyanobacteria, protein, invention, host, promoter, disclosure, species, insecticidal, examiner, cyanobacterium, disclose, encoding, skill, specification, chimeric, bacteria, sequence, transformed, heterologous, comprising, plasmid, enablement, organism, coli, cell, experimentation, obviousness, procaryote, genera

LexisNexis(R) Headnotes

Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness
Patent Law > Jurisdiction & Review > Standards of Review > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN1] Obviousness, within the meaning of *35 U.S.C.S. § 103,* is a legal question which the court independently reviews, though based upon underlying factual findings which the court reviews under the clearly erroneous standard.

Patent Law > Nonobviousness > Elements & Tests > General Overview

[HN2] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under *35 U.S.C.S. § 103* requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

Patent Law > Claims & Specifications > Enablement Requirement > Standards & Tests

[HN3] The first paragraph of *35 U.S.C.S. § 112* requires, inter alia, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is undue.

Patent Law > Claims & Specifications > Enablement Requirement > General Overview
Patent Law > Jurisdiction & Review > Standards of Review > General Overview

[HN4] Enablement is a question of law, which the court independently reviews, although based upon underlying factual findings, which the court reviews for clear error.

Patent Law > Claims & Specifications > Enablement Requirement > General Overview
Patent Law > Claims & Specifications > Description Requirement > General Overview
Patent Law > U.S. Patent & Trademark Office Proceedings > Filing Requirements > General Overview

[HN5] Patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. The disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a predictable factor such as a mechanical or electrical element.

COUNSEL:

Ian C. McLeod, Ian C. McLeod, P.C., of Okemos, Michigan, argued for Appellant.

Teddy S. Gron, Associate Solicitor, Office of the Solicitor, of Arlington, Virginia, argued for Appellee. With him on the brief were Fred E. McKelvey, Solicitor and Richard E. Schafer, Associate Solicitor.

JUDGES:

Rich, Archer, and Mayer, Circuit Judges. Mayer, Circuit Judge, dissenting.

OPINIONBY:

RICH

OPINION:

[*489] RICH, Circuit Judge

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under *35 U.S.C. § 103,* as well as the rejection of claims 1-48 and 50-51 under *35 U.S.C. § 112,* first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part [**2] and reversed in part.

BACKGROUND

A. The Invention

The claimed invention is directed to the use of genetic engineering techniques n1 for production of proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus* proteins over swamps. The spores were environmentally unstable, however, and would

often sink to the bottom of a swamp before being consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle.

n1 Basic vocabulary and techniques for gene cloning and expression have been described in *In re O'Farrell, 853 F.2d 894, 895-99, 7 U.S.P.Q.2D (BNA) 1673, 1674-77 (Fed. Cir. 1988),* and are not repeated here.

[**3]

As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote n2 kingdom, the cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced within [*490] transformed n3 cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.

n2 All living cells can be classified into one of two broad groups, procaryotes and eucaryotes. The procaryotes comprise organisms formed of cells that do not have a distinct nucleus; their DNA floats throughout the cellular cytoplasm. In contrast, the cells of eucaryotic organisms such as man, other animals, plants, protozoa, algae and yeast have a distinct nucleus wherein their DNA resides. [**4]

n3 "Transformed" cyanobacteria are those that have successfully taken up the foreign *Bacillus* DNA such that the DNA information has become a permanent part of the host cyanobacteria, to be replicated as new cyanobacteria are generated.

More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing n4 the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.

N4 "Expression" of a gene refers to the production of the protein which the gene encodes; more specifically, it is the process of transferring information from a gene (which consists of DNA) via messenger RNA to ribosomes where a specific protein is made.

The claims on appeal are 1-48 and 50-52, all claims remaining in the [**5] application. Claim 1 reads:

> 1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:
> (a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and
> (b) at least one DNA fragment coding for an insecticidally active protein produced by a Bacillus strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,

the DNA fragments being linked so that the gene is expressed.

Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers. n5 Independent claim 16 and claims 17-31 which depend therefrom are directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobacterium which expresses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

n5 In the context of the claimed invention, "selectable markers" or "marker genes" refer to antibiotic-resistance conferring DNA fragments, attached to the gene being expressed, which facilitate the selection of successfully transformed cyanobacteria.

[**6]

B. Appellants' Disclosure

In addition to describing the claimed invention in generic terms, appellants' specification discloses two particular species of *Bacillus (B. thuringiensis, B. sphaericus)* as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis, Anacystis, Synechococcus, Agmenellum, Aphanocapsa, Gloecapsa, Nostoc, Anabaena* and *Ffremyllia*) as useful hosts.

The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis*, linked to (2) a particular promoter, the P[L] promoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P[L] promoter.

C. The Prior Art

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal.

The focus of Dzelzkalns, n6 [**7] the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter [*491] sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT). n7 Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

n6 12 *Nucleic Acids Res.* 8917 (1984).

n7 Chloramphenicol is an antibiotic; CAT is an enzyme which destroys chloramphenicol and thus imparts resistance thereto.

Sekar I, n8 Sekar II, n9 and Ganesan n10 collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium, B. subtilis* and *E. coli*.

n8 137 *Biochem. and Biophys. Res. Comm.* 748 (1986). [**8]

n9 33 *Gene* 151 (1985).

n10 189 *Mol. Gen. Genet.* 181 (1983).

Friedberg n11 discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the O[L]P[L] operator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis, Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of over-expressed, highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis* . . . ."

n11 203 *Mol. Gen. Genet.* 505 (1986).

Miller n12 compares [**9] the initiation specificities *in vitro* of DNA-dependent RNA polymerases n13 purified from two different species of cyanobacteria (*Fremyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli*.

n12 140 *J. Bacteriology* 246 (1979).

n13 RNA polymerase, the enzyme responsible for making RNA from DNA, binds at specific nucleotide sequences (promoters) in front of genes in DNA, and then moves through the gene making an RNA molecule that includes the information contained in the gene. Initiation specificity is the ability of the RNA polymerase to initiate this process specifically at a site(s) on the DNA template.

Nierzwicki-Bauer n14 identifies in the cyanobacterium *Anabaena* 7120 the start site for transcription of the gene encoding *rbcL*, the large subunit of the enzyme ribulose-1,5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the [**10] start site does not.

n14 81 *Proc. Natl. Acad. Sci. USA* 5961 (1984).

Chauvat n15 discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.

n15 204 *Mol. Gen. Genet.* 185 (1986).

Reiss n16 studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.

n16 30 *Gene* 211 (1984).

Kolowsky n17 discloses chimeric plasmids designed for transformation of the cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium.

n17 27 *Gene* 289 (1984).

[**11]

Barnes, United States Patent No. *4,695,455*, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

[*492] *D. The Grounds of Rejection*

1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under *35 U.S.C. § 103* based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed [**12] out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus*, and the advantages of expressing such genes in heterologous n18 hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes. In the absence of evidence to the contrary, the examiner contended, the invention as a whole was prima facie obvious.

n18 Denotes different species or organism.

Additional rejections were entered against various groups of dependent claims [**13] which we need not address here. All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above.

The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell, 853 F.2d 894, 7 U.S.P.Q.2D (BNA) 1673 (Fed. Cir. 1988).* In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under *35 U.S.C. § 112,* first paragraph, on the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n) n19 and (z) n20 as support, the examiner took the position that undue experimentation would be required of [**14] the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth of the claims, the limited number of working examples and the limited guidance provided [*493] in the specification. With respect to unpredictability, the examiner stated that

> the cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis, Anacystis, Synechococcus, Agmenellum, Nostoc, Anabaena*, etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera. Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high. . . .

n19 MPEP 706.03(n), "Correspondence of Claim and Disclosure," provides in part:

> In chemical cases, a claim may be so broad as to not be supported by [the] disclosure, in which case it is rejected as unwarranted by the disclosure. . . .

n20 MPEP 706.03(z), "Undue Breadth," provides in part:

> In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol*, 1938 *C.D. 723; 497 O.G. 546.* This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 1940 *C.D. 351; 518 O.G. 255* gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result.". . .

[**15]

The Board affirmed, noting that "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher, 57 C.C.P.A. 1099, 427 F.2d 833, 166 U.S.P.Q. (BNA) 18 (CCPA 1970).*"

OPINION

A. *Obviousness*

We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of *35 U.S.C. § 103.* [HN1] Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff, 919 F.2d 1575, 1577, 16 U.S.P.Q.2D (BNA) 1934, 1935 (Fed. Cir. 1990).*

[HN2] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art [**16] that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q.2D (BNA) 1529, 1531 (Fed. Cir. 1988).* Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes.

The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, [**17] does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (B. *megaterium* and B. *subtilis*) as well as in the bacterium *E. coli.* While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed *bacterial* hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the [**18] PTO contends. [*494] As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae. n21 Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

> n21 *Stedman's Medical Dictionary* 1139 (24th ed. 1982) (definition of "Procaryotae"). Procaryotic organisms are commonly classified according to the following taxonomic hierarchy: Kingdom; Division; Class; Order; Family; Genus; Species. 3 *Bergey's Manual of Systematic Bacteriology* 1601 (1989).

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), [**19] which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also [**20] disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins.

In *O'Farrell*, this court affirmed an obviousness rejection of a claim to a method for producing a "predetermined protein in a stable form" in a transformed bacterial host. *853 F.2d at 895, 7 U.S.P.Q.2d at 1674.* The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three co-inventor-appellants. The main difference [**21] between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id. at 901, 7 U.S.P.Q.2d at 1679.* Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that

> the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.
> . . . . [*495] . . . Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

Id. at 901-02, 7 U.S.P.Q.2d at 1679-80.

In contrast with the situation [**22] in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

B. Enablement

[HN3] The first paragraph of *35 U.S.C. § 112* requires, *inter alia*, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands, 858 F.2d 731, 737, 8 U.S.P.Q.2D (BNA) 1400, 1404 (Fed. Cir. 1988).* That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id. at 736-37, 8 U.S.P.Q.2d at 1404.* [HN4] Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id. at 735, 8 U.S.P.Q.2d at 1402.* [**23]

In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.

The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, [**24] we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.

Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria. *See In re Fisher, 57 C.C.P.A. 1099, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (CCPA 1970)* (the first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification). n22 Accordingly, [*496] we affirm the § 112 rejection as to those claims.

> n22 The enablement rejection in this case was not based upon a post-filing date state of the art, as in *In re Hogan, 559 F.2d 595, 605-07, 194 U.S.P.Q. (BNA) 527, 536-38 (CCPA 1977). See also United States Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1251, 9 U.S.P.Q.2D (BNA) 1461, 1464 (Fed. Cir. 1989)* (citing *Hogan*); *Hormone Research Found., Inc. v. Genentech, Inc., 904 F.2d 1558, 1568-69, 15 U.S.P.Q.2D (BNA) 1039, 1047-48 (Fed. Cir. 1990)* (directing district court, on remand, to consider effect of *Hogan* and *United States Steel* on the enablement analysis of *Fisher*), *cert. dismissed, U.S. , 111 S. Ct. 1434, 113 L. Ed. 2d 485, 59 U.S.L.W. 3687 (1991).* We therefore do not consider the effect of *Hogan* and its progeny on *Fisher's* analysis of when an inventor should be allowed to "dominate the future patentable inventions of others." *Fisher, 427 F.2d at 839, 166 U.S.P.Q. at 24.*

[**25]

In so doing we do *not* imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that [HN5] patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt, 537 F.2d 498, 502-03, 190 U.S.P.Q. (BNA) 214, 218 (CCPA 1976).* However, there must be sufficient disclosure, either through illustrative examples or terminology, n23 to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. *See Fisher, 427 F.2d at 839, 166 U.S.P.Q. at 24.* [**26] In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation.

> n23 The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (CCPA 1971).* How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant. *Id.*

Remaining dependent claim 47 recites a cyanobacterium which expresses the chimeric gene of claim 1, wherein the cyanobacterium is selected from among the genera *Anacystis* and *Synechocystis*. Claim 48, which depends from claim 47, is limited to the cyanobacterium *Synechocystis* 6803. The PTO did not separately address these claims, nor indicate why they should be treated in the same manner as the claims encompassing all types of cyanobacteria. Although these claims are not limited to expression of [**27] genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects. The rejection of claims 47-48 under § 112 will not be sustained.

CONCLUSION

The rejection of claims 1-48 and 50-52 under *35 U.S.C. § 103* is *reversed.* The rejection of claims 1-46 and 50-51 under *35 U.S.C. § 112,* first paragraph, is *affirmed* and the rejection of claims 47 and 48 thereunder is *reversed.*

AFFIRMED-IN-PART, REVERSED-IN-PART.

DISSENTBY:

MAYER

DISSENT:

MAYER, Circuit Judge, dissenting.

An appeal is not a second opportunity to try a case or prosecute a patent application, and we should not allow parties to "undertake to retry the entire case on appeal." *Perini America, Inc. v. Paper Converting Machine Co., 832 F.2d 581, 584, 4 U.S.P.Q.2D (BNA) 1621, 1624 (Fed. Cir. 1987); Eaton Corp. v. Appliance Valves Corp., 790 F.2d 874, 877, 229 U.S.P.Q. (BNA) 668, 671 (Fed. Cir. 1986).* But that is precisely what the court has permitted here. The PTO conducted a thorough examination of the prior art surrounding this patent application and concluded the claims would [**28] have been obvious. The board's decision based on the examiner's answer which comprehensively explains the rejection is persuasive and shows how the evidence supports the legal conclusion that the claims would have been obvious. Yet, the court ignores all this and conducts its own examination, if you will, as though the examiner and board did not exist. Even if I thought this opinion were more persuasive than the board's, I could [*497] not join it because it misperceives the role of the court.

The scope and content of the prior art, the similarity between the prior art and the claims, the level of ordinary skill in the art, and what the prior art teaches are all questions of fact. *Graham v. John Deere Co., 383 U.S. 1, 17, 148 U.S.P.Q. (BNA) 459, 467, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966); Jurgens v. McKasy, 927 F.2d 1552, 1560, 18 U.S.P.Q.2D (BNA) 1031, 1037 (Fed. Cir. 1991).* And "where there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City, 470 U.S. 564, 574, 84 L. Ed. 2d 518, 105 S. Ct. 1504 (1985).* The mere denomination of obviousness as a question of law does not give the court license to decide [**29] the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous. *In re Woodruff, 919 F.2d 1575, 1577, 16 U.S.P.Q.2D (BNA) 1934, 1935 (Fed. Cir. 1990); In re Kulling, 897 F.2d 1147, 1149, 14 U.S.P.Q.2D (BNA) 1056, 1057 (Fed. Cir. 1990).* There may be more than one way to look at the prior art, but on this record we are

bound by the PTO's interpretation of the evidence because it is not clearly erroneous and its conclusion is unassailable. I would affirm on that basis.

LEXSEE 853 F2ND 894

IN RE PATRICK H. O'FARRELL, BARRY A. POLISKY and DAVID H. GELFAND

No. 87-1486

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

853 F.2d 894; 1988 U.S. App. LEXIS 10951; 7 U.S.P.Q.2D (BNA) 1673

August 10, 1988, Decided

PRIOR HISTORY: [**1]

Appealed from: U.S. Patent and Trademark Office Board of Patent Appeals and Interferences.

CASE SUMMARY:

PROCEDURAL POSTURE: Appellants sought review of the decision of U.S. Patent and Trademark Office Board of Patent Appeals and Interferences rejecting appellants' application under *35 U.S.C.S. § 103* because the claimed invention was obvious at the time the invention was made in view of a published paper by two of the coinventors.

OVERVIEW: Appellants alleged that at the time their article was published that there was significant unpredictability in the field of molecular biology so that the article would not have rendered the claimed method of translating heterologous DNA in bacteria obvious to one of ordinary skill in the art. In the alternative, appellants argued that the rejection was founded on the impermissible "obvious to try" standard. The court disagreed, holding that in light of the article, the claimed invention would have been obvious within the meaning of *35 U.S.C.S. § 103*. The article contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful. Appellants foreclosed themselves from obtaining a patent because they published their pioneering studies more than a year before applying for a patent.

OUTCOME: The decision rejecting appellants' patent application was affirmed because the claimed invention was obvious in light of the published paper by two of the three co-inventors prior to filing their patent application.

CORE TERMS: gene, protein, sequence, beta-galactosidase, codon, bacteria, chain, plasmid, invention, nucleotide, heterologous, polypeptide, molecule, cell, amino acids, translated, ribosomal, inserted, messenger, translation, lactose, readthrough, indigenous, peptide, coding, coli, patent, predetermined, transformed, bacterium

LexisNexis(R) Headnotes

Civil Procedure > Trials > Judgment as Matter of Law
Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN1] Obviousness under *35 U.S.C.S. § 103* is a question of law.

Patent Law > Claims & Specifications > Enablement Requirement > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN2] An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any.

Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > General Overview

Patent Law > Nonobviousness > Evidence & Procedure > General Overview
Patent Law > Claims & Specifications > Enablement Requirement > General Overview
[HN3] Keeping the four statutory factors in mind and considering all of the evidence, the court must determine the correctness of the board's legal determination that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made.

Patent Law > Nonobviousness > Elements & Tests > General Overview
[HN4] Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious.

COUNSEL:

J. Bruce McCubbrey, Fitch, Even, Tabin & Flannery, of San Francisco, California, argued for Appellant. Virginia H. Meyer, Fitch, Even, Tabin & Flannery, of San Francisco, California, was on the brief for Appellant.

Harris A. Pitlick, Associate Solicitor, of Arlington, Virginia, argued for Appellee. With him on the brief were Joseph F. Nakamura, Solicitor and Fred E. McKelvey, Deputy Solicitor.

JUDGES:

Markey, Chief Judge, Rich and Nies, Circuit Judges.

OPINIONBY:

RICH

OPINION:

[*895] RICH, Circuit Judge.

This appeal is from the decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences (board) affirming the patent examiner's final rejection of patent application Serial No. 180,424, entitled "Method and Hybrid Vector for Regulating Translation of Heterologous DNA in Bacteria." The application was rejected under *35 U.S.C. § 103* on the ground that the claimed invention would have been obvious at the time the invention was made in view of a published paper by two of the three coinventors, and a publication by Bahl, [**2] Marians & Wu, 1 *Gene* 81 (1976) (Bahl). We affirm.

The claimed invention is from the developing new field of genetic engineering. A broad claim on appeal reads:

> Claim 1. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria comprising, providing a cloning vector which includes at least a substantial portion of a gene which is indigenous to the host species of bacteria and is functionally transcribed and translated in that species, said substantial portion of said indigenous gene further including the regulatory DNA sequences for RNA synthesis and protein synthesis but lacking the normal gene termination signal, and linking a natural or synthetic heterologous gene encoding said predetermined protein to said indigenous gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of said indigenous gene portion so that readthrough can occur from said indigenous gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused [**3] protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Illustrative embodiments are defined in more specific claims. For example:

> Claim 2. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria, comprising, providing an *E. coli* plasmid having an operator, a promoter, a site for the initiation of translation, and at least a substantial portion of the beta-galactosidase gene of the *E. coli* lactose operon, said substantial portion of said beta-galactosidase gene being under the control of said operator, promoter and site for initiation of translation, said substantial portion of said beta-

galactosidase gene lacking the normal gene termination signal, and linking a heterologous gene encoding said predetermined protein to said beta-galactosidase gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of the said beta-galactosidase gene portion so that readthrough can occur from said beta-galactosidase gene portion into said [**4] heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Claim 3. The method of Claim 2 wherein said *E. coli* plasmid comprises the plasmid designated pBGP120.

Although the terms in these claims would be familiar to those of ordinary skill in genetic engineering, they employ a bewildering vocabulary new to those who are not versed in molecular biology. An understanding of the science and technology on which these claims are based is essential before one can analyze and explain whether the claimed invention would have been obvious in light of the prior art.

I. *Background* n1

n1 Basic background information about molecular biology and genetic engineering, can be found in Alberts, Bray, Lewis, Raff, Roberts & Watson, *The Molecular Biology of the Cell*, 1-253, 385-481 (1983) [hereinafter *The Cell*]; Watson, Hopkins, Roberts, Steitz & Weiner, *The Molecular Biology of the Gene*, Vol. 1 (4th ed., 1987) 3-502 [hereinafter *The Gene*]. These standard textbooks were used to supplement the information in the glossary supplied by appellants. The description here is necessarily simplified and omits important facts and concepts that are not necessary for the analysis of this case.

[**5]

Proteins are biological molecules of enormous importance. Proteins include enzymes [*896] that catalyze biochemical reactions, major structural materials of the animal body, and many hormones. Numerous patents and applications for patents in the field of biotechnology involve specific proteins or methods for making and using proteins. Many valuable proteins occur in nature only in minute quantities, or are difficult to purify from natural sources. Therefore, a goal of many biotechnology projects, including appellants' claimed invention, is to devise methods to synthesize useful quantities of specific proteins by controlling the mechanism by which living cells make proteins.

The basic organization of all proteins is the same. Proteins are large polymeric molecules consisting of chains of smaller building blocks, called *amino acids*, that are linked together covalently. n2 The chemical bonds linking amino acids together are called *peptide* bonds, so proteins are also called *polypeptides*. n3 It is the exact sequence in which the amino acids are strung together in a polypeptide chain that determines the identity of a protein and its chemical characteristics. n4 Although [**6] there are only 20 amino acids, they are strung together in different orders to produce the hundreds of thousands of proteins found in nature.

n2 There are twenty amino acids: alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, and histidine.

n3 Proteins are often loosely called *peptides*, but technically proteins are only the larger peptides with chains of at least 50 amino acids, and more typically hundreds of amino acids. Some proteins consist of several polypeptide chains bound together covalently or noncovalently. The term "peptide" is broader than "protein" and also includes small chains of amino acids linked by peptide bonds, some as small as two amino acids. Certain small peptides have commercial or medical significance.

n4 Polypeptide chains fold up into complex 3-dimensional shapes. It is the shape that actually determines many chemical properties of the protein. However, the configuration of a protein molecule is determined by its amino acid sequence. *The Cell* at 111-12; *The Gene* at 50-54.

[**7]

To make a protein molecule, a cell needs information about the sequence in which the amino acids must be assembled. The cell uses a long polymeric molecule, DNA (deoxyriboneucleic acid), to store this information. The subunits of the DNA chain are called

nucleotides. A nucleotide consists of a nitrogen-containing ring compound (called a *base*) linked to a 5-carbon sugar that has a phosphate group attached. n5 DNA is composed of only four nucleotides. They differ from each other in the base region of the molecule. The four bases of these subunits are adenine, guanine, cytosine, and thymine (abbreviated respectively as A, G, C and T). The sequence of these bases along the DNA molecule specifies which amino acids will be inserted in sequence into the polypeptide chain of a protein.

n5 The sugar in DNA is deoxyribose, while the sugar in RNA, *infra*, is ribose. The sugar and phosphate groups are linked covalently to those of adjacent nucleotides to form the backbone of the long unbranched DNA molecule. The bases project from the chain, and serve as the "alphabet" of the genetic code.

DNA molecules actually consist of two chains tightly entwined as a double helix. The chains are not identical but instead are complementary: each A on one chain is paired with a T on the other chain, and each C has a corresponding G. The chains are held together by noncovalent bonds between these complementary bases. This double helical structure plays an essential role in the replication of DNA and the transmission of genetic information. *See generally The Cell* at 98-106; *The Gene* at 65-79. However, the information of only one strand is used for directing protein synthesis, and it is not necessary to discuss the implication of the double-stranded structure of DNA here. RNA molecules, *infra*, are single stranded.

[**8]

DNA molecules do not participate directly in the synthesis of proteins. DNA acts as a permanent "blueprint" of all of the [*897] genetic information in the cell, and exists mainly in extremely long strands (called *chromosomes*) containing information coding for the sequences of many proteins, most of which are not being synthesized at any particular moment. The region of DNA on the chromosome that codes for the sequence of a single polypeptide is called a *gene*. n6 In order to *express* a gene (the process whereby the information in a gene is used to synthesize new protein), a copy of the gene is first made as a molecule of RNA (ribonucleic acid).

n6 Chromosomes also contain regions of DNA that are not part of genes, i.e., do not code for the sequence of amino acids in proteins. These include sections of DNA adjacent to genes that are involved in the control of transcription, *infra*, and regions of unknown function.

RNA is a molecule that closely resembles DNA. It differs, however, in that [**9] it contains a different sugar (ribose instead of deoxyribose) and the base thymine (T) of DNA is replaced in RNA by the structurally similar base, uracil (U). Making an RNA copy of DNA is called *transcription*. The transcribed RNA copy contains sequences of A, U, C, and G that carry the same information as the sequence of A, T, C, and G in the DNA. That RNA molecule, called *messenger RNA*, then moves to a location in the cell where proteins are synthesized.

The code whereby a sequence of nucleotides along an RNA molecule is translated into a sequence of amino acids in a protein (i.e., the "genetic code") is based on serially reading groups of three adjacent nucleotides. Each combination of three adjacent nucleotides, called a *codon*, specifies a particular amino acid. For example, the codon U-G-G in a messenger RNA molecule specifies that there will be a tryptophan molecule in the corresponding location in the corresponding polypeptide. The four bases A, G, C and U can be combined as triplets in 64 different ways, but there are only 20 amino acids to be coded. Thus, most amino acids are coded for by more than one codon. For example, both U-A-U and U-A-C code for tyrosine, [**10] and there are six different codons that code for leucine. There are also three codons that do not code for any amino acid (namely, U-A-A, U-G-A, and U-A-G). Like periods at the end of a sentence, these sequences signal the end of the polypeptide chain, and they are therefore called *stop codons*.

The cellular machinery involved in synthesizing proteins is quite complicated, and centers around large structures called *ribosomes* that bind to the messenger RNA. The ribosomes and associated molecules "read" the information in the messenger RNA molecule, literally shifting along the strand of RNA three nucleotides at a time, adding the amino acid specified by that codon to a growing polypeptide chain that is also attached to the ribosome. When a stop codon is reached, the polypeptide chain is complete and detaches from the ribosome.

The conversion of the information from a sequence of codons in an RNA molecule into the sequence of amino acids in a newly synthesized polypeptide is called *translation*. A messenger RNA molecule is typically reused to make many copies of the same protein. Synthesis of a protein is usually terminated by destroying

the messenger RNA. (The information [**11] for making more of that protein remains stored in DNA in the chromosomes.)

The translation of messenger RNA begins at a specific sequence of nucleotides that bind the RNA to the ribosome and specify which is the first codon that is to be translated. Translation then proceeds by reading nucleotides, three at a time, until a stop codon is reached. If some error were to occur that shifts the frame in which the nucleotides are read by one or two nucleotides, all of the codons after this shift would be misread. For example, the sequence of codons [. . . *C-U-C-A-G-C-G-U-U-A-C-C-A*. . .] codes for the chain of amino acids [. .. leucine-serine-valine-threonine-. . .]. If the reading of these groups of three nucleotides is displaced by one nucleotide, such as [. . . *C-U-C-A-G-C-G-U-U-A-C-C-A* . . .], the resulting peptide chain would consist of [*898] [. . . serine-alanine-leucine-proline. . .]. This would be an entirely different peptide, and most probably an undesirable and useless one. Synthesis of a particular protein requires that the correct register or *reading frame* be maintained as the codons in the RNA are translated.

The function of messenger RNA is to carry [**12] genetic information (transcribed from DNA) to the protein synthetic machinery of a cell where its information is translated into the amino acid sequence of a protein. However, some kinds of RNA have other roles. For example, ribosomes contain several large strands of RNA that serve a structural function (*ribosomal RNA*). Chromosomes contain regions of DNA that code for the nucleotide sequences of structural RNAs and these sequences are transcribed to manufacture those RNAs. The DNA sequences coding for structural RNAs are still called genes even though the nucleotide sequence of the structural RNA is never translated into protein.

Man, other animals, plants, protozoa, and yeast are *eucaryotic* (or eukaryotic) organisms: their DNA is packaged in chromosomes in a special compartment of the cell, the nucleus. Bacteria (*procaryotic* or prokaryotic organisms) have a different organization. Their DNA, usually a circular loop, is not contained in any specialized compartment. Despite the incredible differences between them, all organisms, whether eucaryote or procaryote, whether man or mouse or lowly bacterium, use the same molecular rules to make proteins under the control of genes. [**13] In all organisms, codons in DNA are transcribed into codons in RNA which is translated on ribosomes into polypeptides according to the same genetic code. Thus, if a gene from a man is transferred into a bacterium, the bacterium can manufacture the human protein. Since most commercially valuable proteins come from man or other eucaryotes while bacteria are essentially little biochemical factories that can be grown in huge quantities, one strategy for manufacturing a desired protein (for example, insulin) is to transfer the gene coding for the protein from the eucaryotic cell where the gene normally occurs into a bacterium.

Bacteria containing genes from a foreign source (*heterologous* genes) integrated into their own genetic makeup are said to be *transformed.* When transformed bacteria grow and divide, the inserted heterologous genes, like all the other genes that are normally present in the bacterium (*indigenous* genes), are replicated and passed on to succeeding generations. One can produce large quantities of transformed bacteria that contain transplanted heterologous genes. The process of making large quantities of identical copies of a gene (or other fragment of DNA) [**14] by introducing it into procaryotic cells and then growing those cells is called *cloning* the gene. After growing sufficient quantities of the transformed bacteria, the biotechnologist must induce the transformed bacteria to *express* the cloned gene and make useful quantities of the protein. This is the purpose of the claimed invention.

In order to make a selected protein by expressing its cloned gene in bacteria, several technical hurdles must be overcome. First the gene coding for the specific protein must be isolated for cloning. This is a formidable task, but recombinant DNA technology has armed the genetic engineer with a variety of techniques to accomplish it. n7 Next the isolated gene must be introduced into the host bacterium. This can be done by incorporating the gene into a cloning vector. A *cloning vector* is a piece of DNA that can be introduced into bacteria and will then replicate itself as the bacterial cells grow and divide. Bacteriophage (viruses that infect bacteria) can be used as cloning vectors, but plasmids were the type used by appellants. A *plasmid* is a small circular loop of DNA found in bacteria, separate from the chromosome, that replicates [**15] like a chromosome. It is like a tiny auxilliary chromosome containing only a few genes. Because of their small size, plasmids are convenient for the molecular biologist to isolate and work with. Recombinant DNA technology can be used to modify plasmids by splicing in cloned eucaryotic [*899] genes and other useful segments of DNA containing control sequences. Short pieces of DNA can even be designed to have desired nucleotide sequences, synthesized chemically, and spliced into the plasmid. One use of such chemically synthesized linkers is to insure that the inserted gene has the same reading frame as the rest of the plasmid; this is a teaching of the Bahl reference cited against appellants. A plasmid constructed by the molecular geneticist can be inserted into bacteria, where it replicates as the bacteria grow.

n7 *See The Cell* at 185-194; *The Gene* at 208-10.

Even after a cloned heterologous gene has been successfully inserted into bacteria using a plasmid as a cloning vector, and replicates as [**16] the bacteria grow, there is no guarantee that the gene will be expressed, i.e., transcribed and translated into protein. A bacterium such as *E. coli* (the species of bacterium used by appellants) has genes for several thousand proteins. At any given moment many of those genes are not expressed at all. The genetic engineer needs a method to "turn on" the cloned gene and force it to be expressed. This is the problem appellants worked to solve.

II. *Prior art*

Appellants sought to control the expression of cloned heterologous genes inserted into bacteria. They reported the results of their early efforts in a publication, the three authors of which included two of the three coinventor-appellants (the Polisky reference n8), that is undisputed prior art against them. Their strategy was to link the foreign gene to a highly regulated indigenous gene. Turning on expression of the indigenous gene by normal control mechanisms of the host would cause expression of the linked heterologous gene.

n8 Polisky, Bishop & Gelfand, *A plasmid cloning vehicle allowing regulated expression of eukaryotic DNA in bacteria*, 73 Proc. Nat'l Acad. Sci. USA 3900 (1976).

[**17]

As a controllable indigenous gene, the researchers chose a gene in the bacterium *E. coli* that makes beta-galactosidase. *Beta-galactosidase* is an enzyme needed to digest the sugar, lactose (milk sugar). When *E. coli* grows in a medium that contains no lactose, it does not make beta-galactosidase. If lactose is added to the medium, the gene coding for beta-galactosidase is expressed. The bacterial cell makes beta-galactosidase and is then able to use lactose as a food source. When lactose is no longer available, the cell again stops expressing the gene for beta-galactosidase.

The molecular mechanisms through which the presence of lactose turns on expression of the beta-galactosidase gene has been studied in detail, and is one of the best understood examples of how gene expression is regulated on the molecular level. The beta-galactosidase gene is controlled by segments of DNA adjacent to the gene. These *regulatory DNA sequences* (the general term used in Claim 1) include the *operator* and *promoter* sequences (specified in Claim 2). n9 The researchers constructed a plasmid containing the beta-galactosidase gene with its operator and promoter. This gene (with its [**18] regulatory sequences) was removed from the chromosome of *E. coli* where it is normally found and was transplanted to a plasmid that could be conveniently manipulated.

n9 The *promoter* is a sequence of nucleotides where the enzyme that synthesizes RNA, *RNA polymerase*, attaches to the DNA to start the transcription of the beta-galactosidase gene. The *operator* is an overlapping DNA sequence that binds a small protein present in the cell, the lactose repressor protein. The lactose repressor protein binds to the operator and physically blocks the RNA polymerase from properly attaching to the promoter so that transcription cannot proceed. Lactose molecules interact with the lactose repressor protein and cause it to change its shape; after this change in shape it moves out of the way and no longer prevents the RNA polymerase from binding to the promoter. Messenger RNA coding for beta-galactosidase can then be transcribed. *See generally The Cell* at 438-39; *The Gene* at 474-80.

Restriction endonucleases [**19] are useful tools in genetic engineering. These enzymes cut strands of DNA, but only at places where a specific sequence of nucleotides is present. For example, one restriction endonuclease, called *EcoRI*, cuts DNA only at sites where the nucleotide sequence is [. . .-G-A-A-T-T-C-. . .]. With restriction [*900] enzymes the genetic engineer can cut a strand of DNA at very specific sites into just a few pieces. With the help of "repair" enzymes, other pieces of DNA can be spliced onto the cut ends. The investigators found that the plasmid which they had constructed contained only two sequences that were cut by EcoRI. They were able to eliminate one of these sites that was unwanted. They were then left with a plasmid containing the beta-galactosidase gene with its regulatory sequences, and a single EcoRI site that was within the beta-galactosidase gene and close to its stop codon. They named this plasmid that they had constructed pBGP120.

The next step was to cut the plasmid open at its EcoRI site and insert a heterologous gene from another organism. The particular heterologous gene they chose to splice in was a segment of DNA from a frog that coded for ribosomal RNA. The frog [**20] gene was chosen as a test gene for reasons of convenience and availability. The new plasmid created by inserting the frog gene was similar to pBGP120, but its beta-galactosidase gene was incomplete. Some codons including the stop codon were

missing from its end, which instead continued on with the sequence of the frog ribosomal RNA gene. The investigators named this new plasmid pBGP123. They inserted this plasmid back into *E. coli* and grew sufficient quantities for study. They then fed the *E. coli* with lactose. As they had intended, the lactose turned on transcription of the beta-galactosidase gene in the plasmid. RNA polymerase moved along the plasmid producing a strange new kind of RNA: Each long strand of RNA first contained codons for the messenger RNA for beta-galactosidase and then continued without interruption with the codons for the frog ribosomal RNA. Thus, there was *readthrough* transcription in which the RNA polymerase first transcribed the indigenous (beta-galactosidase) gene and then "read through," i.e., continued into and through the adjacent heterologous (frog ribosomal RNA) gene. Although the RNA produced was a hybrid, it nevertheless contained a nucleotide [**21] sequence dictated by DNA from a frog. The researchers had achieved the first controlled transcription of an animal gene inside a bacterium.

The researchers had used a gene coding for a ribosomal RNA as their heterologous test gene. Ribosomal RNA is not normally translated into protein. Nevertheless, they were obviously interested in using their approach to make heterologous proteins in bacteria. They therefore examined the beta-galactosidase made by their transformed bacteria. Patrick O'Farrell, who was not a coauthor of the Polisky paper but was to become a coinventor in the patent application, joined as a collaborator. They found that beta-galactosidase from the transformed bacteria had a higher molecular weight than was normal. They concluded that the bacteria must have used their strange new hybrid RNA like any other messenger RNA and translated it into protein. When the machinery of protein synthesis reached the premature end of the sequence coding for beta-galactosidase it continued right on, three nucleotides at a time, adding whatever amino acid was coded for by those nucleotides, until a triplet was reached with the sequence of a stop codon. The resulting polypeptide chains [**22] had more amino acids than normal beta-galactosidase, and thus a higher molecular weight. The researchers published their preliminary results in the Polisky article. They wrote:

> If the normal translational stop signals for [beta]-galactosidase are missing in pBGP120, in-phase translational readthrough into adjacent inserted sequences might occur, resulting in a significant increase in the size of the [beta]-galactosidase polypeptide subunit. In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of *Xenopus* [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

Polisky at 3904.

Since ribosomal RNA is never translated in normal cells, the polypeptide chain produced [*901] by translating that chain was not a naturally occuring, identified protein. The authors of the Polisky paper explicitly pointed out that if one were to insert a heterologous gene coding for a protein into their [**23] plasmid, it should produce a "fused protein" consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain:

> It would be interesting to examine the expression of a normally translated eukaryotic sequence in pBGP120. If an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide. In the absence of an independent ribosome binding site, the eukaryotic sequence would be translated to yield a peptide covalently linked to [beta]-galactosidase. The extent of readthrough translation under *lac* control will depend on the number of translatable codons between the EcoRI site and the first in-phase nonsense [i.e., stop] codon in the inserted sequence.

Id.

III. *The Claimed Invention*

Referring back to Claims 1 through 3, it can be seen that virtually everything in the claims was present in the prior art Polisky article. The main difference is that in Polisky the heterologous gene was a gene [**24] for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. Ribosomal RNA gene is not normally translated into protein, so expression of the heterologous gene was studied mainly

in terms of transcription into RNA. Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, "a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.

Appellants reduced their invention to practice some time in 1976 and reported their results in a paper that was published in 1978. n10 During 1977 they communicated their results to another group of researchers who used the readthrough translation approach to achieve the first synthesis of a human protein in bacteria. n11 Appellants filed an application to patent their [**25] invention on August 9, 1978, of which the application on appeal is a division.

n10 O'Farrell, Polisky & Gelfand, *Regulated expression by readthrough translation from a plasmid-encoded beta-galactosidase*, 134 J. Bacteriol. 645 (1978). The heterologous genes expressed in these studies were not predetermined, but were instead unidentified genes of unknown origin. The authors speculated that they were probably genes from *E. coli* that were contaminants in the source of beta-galactosidase genes. *Id.* at 648.

n11 Itakura, Hirose, Crea, Riggs, Heynecker, Bolivar & Boyer, *Expression in Escherichia coli of a chemically synthesized gene for the hormone somatostatin*, 198 Science 1056 (1977). A pioneering accomplishment of the Itakura group is that the gene was not from a human source, but instead was entirely synthesized in the laboratory using chemical methods. It is not clear whether the appellants communicated only the results reported in the Polisky publication or whether they communicated the complete claimed invention.

[**26]

IV. *The Obviousness Rejection*

The application was rejected under *35 U.S.C. § 103.* The position of the examiner and the Board is, simply, that so much of the appellant's method was revealed in the Polisky reference that making a protein by substituting its gene for the ribosomal RNA gene in Polisky (as suggested by Polisky) would have been obvious to one of ordinary skill in the art at the time that the invention was made.

The claims specify that the heterologous gene should be inserted into the plasmid in the same orientation and with the same reading frame as the preceding portion of [*902] the indigenous gene. In view of this limitation, the § 103 rejection was based either on Polisky alone (supplemented by the fact that the importance of orientation and reading frame was well known in the prior art) or in combination with the Bahl reference which describes a general method for inserting a piece of chemically synthesized DNA into a plasmid. Bahl teaches that this technique could be used to shift the sequence of DNA inserted into a plasmid into the proper [**27] reading frame.

Appellants argue that at the time the Polisky article was published, there was significant unpredictability in the field of molecular biology so that the Polisky article would not have rendered the claimed method obvious to one of ordinary skill in the art. Even though there was speculation in the article that genes coding for proteins could be substituted for the ribosomal RNA gene and would be expressed as readthrough translation into the protein, this had never been done. Appellants say that it was not yet certain whether a heterologous protein could actually be produced in bacteria, and if it could, whether additional mechanisms or methods would be required. They contend that without such certainty the predictions in the Polisky paper, which hindsight now shows to have been correct, were merely invitations to those skilled in the art to try to make the claimed invention. They argue that the rejection amounts to the application of a standard of "obvious to try" to the field of molecular biology, a standard which this court and its predecessors have repeatedly rejected as improper grounds for a § 103 rejection. *E.g., In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988);* [**28] *In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); In re Merck & Co., Inc., 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986); In re Antonie, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977).*

[HN1] Obviousness under § 103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597* (Fed. Cir.), *cert. denied, 481 U.S. 1052, 107 S. Ct. 2187, 95 L. Ed. 2d 843 (1987).* [HN2] An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966). See, e.g., Custom*

Accessories, Inc. v. Jeffrey-Allan Indus., 807 F.2d 955, 958, 1 USPQ2d 1196, 1197 (Fed. Cir. 1986). [**29] The scope and content of the prior art and the differences between the prior art and the claimed invention have been examined in sections II and III, *supra.* Appellants say that in 1976 those of ordinary skill in the arts of molecular biology and recombinant DNA technology were research scientists who had "extraordinary skill in relevant arts" and "were among the brightest biologists in the world." Objective evidence of nonobviousness was not argued.

[HN3] With the statutory factors as expounded by *Graham* in mind and considering all of the evidence, this court must determine the correctness of the board's legal determination that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. We agree with the board that appellant's claimed invention would have been obvious in light of the Polisky reference alone or in combination with Bahl within the meaning of § 103. Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed [**30] invention, and evidence suggesting that it would be successful.

Appellants argue that after the publication of Polisky, successful synthesis of protein was still uncertain. They belittle the predictive value of the observation that expression of the transcribed RNA in Polisky produced beta-galactosidase with a greater than normal molecular weight, arguing that since ribosomal RNA is not normally translated, the polypeptide chains that were added to the end of the beta-galactosidase [*903] were "junk" or "nonsense" proteins. This characterization ignores the clear implications of the reported observations. The Polisky study directly proved that a readthrough transcript messenger RNA had been produced. The preliminary observation showed that this messenger RNA was read and used for successful translation. It was well known in the art that ribosomal RNA was made of the same nucleotides as messenger RNA, that any sequence of nucleotides could be read in groups of three as codons, and that reading these codons should specify a polypeptide chain that would elongate until a stop codon was encountered. The preliminary observations thus showed that codons beyond the end of the beta-galactosidase [**31] gene were being translated into peptide chains. This would reasonably suggest to one skilled in the art that if the codons inserted beyond the end of the beta-galactosidase gene coded for a "predetermined protein," that protein would be produced. In other words, it would have been obvious and reasonable to conclude from the observation reported in Polisky that since nonsense RNA produced nonsense polypeptides, if meaningful RNA was inserted instead of ribosomal RNA, useful protein would be the result. The relative shortness of the added chains is also not a source of uncertainty, since one skilled in the art would have known that a random sequence of nucleotides would produce a stop codon before the chain got too long. n12

n12 The patent application indicates that chains as long as 60 amino acids were added, which is hardly a trivial length of polypeptide.

Appellants complain that since predetermined proteins had not yet been produced in transformed bacteria, there was uncertainty as to whether this could [**32] be done, and that the rejection is thus founded on an impermissible "obvious to try" standard. It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under § 103. However, the meaning of this maxim is sometimes lost. Any invention that would in fact have been obvious under § 103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?

The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *E.g., In re Geiger, 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981);* [**33] *In re Antonie, 559 F.2d at 621, 195 USPQ at 8-9.* In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986), cert. denied, 480 U.S. 947, 107 S. Ct. 1606, 94 L. Ed. 2d 792 (1987); In re Tomlinson, 53 C.C.P.A. 1421, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).* Neither of these situations applies here.

[HN4] Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute

predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for [**34] showing that the invention, although apparently obvious, was in law nonobvious. *In re Merck & Co., 800 F.2d at 1098, 231 USPQ at 380; Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1461,* [*904] *221 USPQ 481, 488 (Fed. Cir. 1984); In re Papesch, 50 C.C.P.A. 1084, 315 F.2d 381, 386-87, 137 USPQ 43, 47-48 (CCPA 1963).* For obviousness under § 103, all that is required is a reasonable expectation of success. *In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); In re Clinton, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976).* The information in the Polisky reference, when combined with the Bahl reference provided such a reasonable expectation of success.

Appellants published their pioneering studies of the expression of frog ribosomal RNA genes in bacteria more than a year before they applied for a patent. After providing virtually all of their method to the public without applying for a patent within a year, they foreclosed themselves from obtaining a patent on a method that would have been obvious from their publication to those of ordinary [**35] skill in the art, with or without the disclosures of other prior art. The decision of the board is

AFFIRMED.

LEXSEE 933 F2ND 982

In Re JEFFREY B. GORMAN and MARILYN KATZ

No. 90-1362

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

933 F.2d 982; 1991 U.S. App. LEXIS 9421; 18 U.S.P.Q.2D (BNA) 1885

May 13, 1991, Decided

PRIOR HISTORY: [**1] Appealed from U.S. Patent & Trademark Office Board of Patent Appeals & Interferences.

DISPOSITION:

Affirmed.

CASE SUMMARY:

PROCEDURAL POSTURE: Applicants appealed from decision of the United States Patent & Trademark Office Board of Patent Appeals & Interferences that denied patentability of all claims in their patent application.

OVERVIEW: Applicants invented a composite candy sucker on a stick that was molded in shape of a human thumb. Liquid candy was poured into a mold. The end was sealed with an edible plug of bubble or chewing gum or chocolate or food-grade wax. The mold was removable and was described as a toy and novelty item. Each element of applicants' claimed invention was prior art, separately or in sub-combination. Applicants argued that their invention should not have been rejected for obviousness under *35 U.S.C.S. § 103* because it was necessary to combine teachings of a large number of references. The court found that the large number of references did not negate the obviousness of the combination. The claim elements appeared in prior art in same configurations, served the same functions, and achieved the results suggested in prior art. The court concluded that the claimed invention as a whole was obvious in terms of *35 U.S.C.S. § 103.*

OUTCOME: The decision was affirmed because each element of applicants' claimed invention existed in prior art, separately or in sub-combination.

CORE TERMS: candy, mold, invention, flexible, rigid, plug, stick, comprising, obviousness, ice cream, thumb-shaped, shell, elastomeric, extending, hardened, teaching, joint-shaped, vertical, upper, axis, confection, wrapper, chewing gum, plastic, opening, thumb, lobes, seal, large number, downwardly

LexisNexis(R) Headnotes

Patent Law > Nonobviousness > Elements & Tests > General Overview

[HN1] The criterion to support a rejection for obviousness under *35 U.S.C.S. § 103* is not the number of references, but what they would have meant to a person of ordinary skill in the field of the invention.

Patent Law > Inequitable Conduct > Effect, Materiality & Scienter > General Overview

Patent Law > Claims & Specifications > Enablement Requirement > General Overview

Patent Law > Nonobviousness > Elements & Tests > General Overview

[HN2] Determination of whether a new combination of known elements would have been obvious to one of ordinary skill depends on various factors, including whether the elements exist in analogous art, that is, art that is reasonably pertinent to the problem with which the inventor is concerned. When the references are all in the same or analogous fields, knowledge thereof by a hypothetical person of ordinary skill is presumed, and the test is whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention.

Patent Law > Nonobviousness > Elements & Tests > Hindsight
Patent Law > Inequitable Conduct > General Overview
Patent Law > Nonobviousness > Evidence & Procedure > General Overview
[HN3] When it is necessary to select elements of various teachings in order to form claimed invention, a court ascertains whether there is any suggestion or motivation in prior art to make selection made by applicant. Obviousness can not be established by combining teachings of prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. The extent to which such suggestion must be explicit in, or may be fairly inferred from, references, is decided on facts of each case, in light of prior art and its relationship to applicant's invention. As in all determinations under *35 U.S.C.S. § 103,* decisionmaker must bring judgment to bear. It is impermissible, however, simply to engage in hindsight reconstruction of claimed invention, using applicant's structure as template and selecting elements from references to fill gaps. References themselves must provide some teaching whereby applicant's combination would have been obvious.

Patent Law > Nonobviousness > Elements & Tests > Hindsight
Patent Law > U.S. Patent & Trademark Office Proceedings > General Overview
Patent Law > Anticipation & Novelty > General Overview
[HN4] A claim that is narrowly and specifically drawn must nevertheless meet the requirements of *35 U.S.C.S. § 103.* The mere fact that a claim recites in detail all of the features of an invention (i.e., is a picture claim) is never, in itself, justification for the allowance of such a claim.

COUNSEL:

Thomas W. Tolpin, of Highland Park, Illinois, argued for Appellant.

Teddy S. Gron, Associate Solicitor, Office of the Solicitor, of Arlington, Virginia, argued for Appellee. With him on the brief was Fred E. McKelvey, Solicitor.

JUDGES:

Rich, Newman, and Rader, Circuit Judges.

OPINIONBY:

NEWMAN

OPINION:

[*983] NEWMAN, Circuit Judge

Jeffrey B. Gorman and Marilyn Katz (hereinafter "Gorman") appeal the decision of the United States Patent and Trademark Office, Board of Patent Appeals and Interferences (the "Board") denying patentability to all the claims of Gorman's patent application Serial No. 06/882,480, entitled "Composite Food Product." We affirm.

The Invention

The claimed invention is a composite candy sucker on a stick, molded in an elastomeric mold in the shape of a human thumb. During the manufacturing process liquid candy is poured into the mold, and an edible plug of bubble or chewing gum or chocolate or food-grade wax is poured into the mold after the candy has hardened, serving as a seal for the end portion of the candy. A paper or plastic disc abuts and covers the plug. The mold serves as a cover that can be removed from the candy by [**2] means of protruding flanges. The cover is described as a "toy and novelty item".

Figure 1 shows the invention in the form in which it is marketed. Figure 2 shows the cover partially removed to reveal the candy portion (12) and the chewable or edible plug (58):

[*984] [SEE ILLUSTRATION IN ORIGINAL]

The claims describe the product in detail, as is apparent from claim 16, the claim pressed by Gorman in this appeal:

> 16. A composite food product, comprising:
>
> a candy core, said candy core being in a generally liquified form when formulated, heated, blended and poured into a mold and in a substantially thumb-shaped hardened form when cooled and removed from said mold;
>
> said thumb-shaped hardened form comprising said candy core positioned along a vertical axis and comprising a rigid joint-shaped portion, a rigid upper portion extending upwardly from said rigid joint-shaped portion along said vertical axis, and a rigid lower portion extending downwardly from said rigid joint-shaped portion along said vertical axis, said upper portion having a rigid finger nail-shaped portion with an upper rigid tip providing a rigid top end of said thumb-shaped hardened form and a rigid convex back extending rearwardly [**3]

and downwardly from said rigid tip, and said rigid lower portion having a rigid bottom end and defining a recessed opening comprising a handle-receiving socket about said vertical axis;

a removable resilient shell comprising a substantially thumb-shaped, elastomeric material selected from the group consisting of rubber and flexible plastic, said shell providing

a mold for receiving and molding said liquified candy form,

[*985] a removable outer protective cover positioned about and covering said hardened form comprising said candy core, and

a toy and novelty item for placement upon the thumb of the user when removed from said hardened form comprising said candy core;

said thumb-shaped elastomeric material comprising said removable resilient shell comprising a flexible joint-shaped portion, a flexible upper portion extending upwardly from said flexible joint-shaped portion along said vertical axis, and a flexible lower portion extending downwardly from said flexible joint-shaped portion along said vertical axis, said upper portion having a flexible finger nail-shaped portion with an upper flexible tip providing a flexible top end of said shell and a flexible convex back extending rearwardly [**4] and downwardly from said flexible tip, and said flexible lower portion having an enlarged open ended diverging base, said base having a larger circumference and transverse cross-sectional area than other portions of said shell and providing the bottom of said shell, said open ended based defining a plug-receiving chamber and an access opening for entrance of said liquified form and discharge of said hardened candy form, and a set of substantially symmetrical arcuate lobes extending radially outwardly from said base, said lobes being circumferentially spaced from each other and providing manually grippable flange portions to facilitate manual removal of said shell from said core;

a plug positioned in said plug-receiving chamber adjacent said bottom of said shell, said plug abutting against the bottom of said core and providing a cap for substantially plugging and sealing the open end of said mold and cover to help enclose said candy core, and said plug comprising a food grade material selected from the group consisting of bubble gum, chewing gum, chocolate, and food grade wax;

a handle having a connecting portion connected to said plug and said candy core and positioned in said plug-receiving [**5] opening and having a manually grippable handle portion extending downward from said connecting portion along said vertical axis; and

a substantially planar annular disk for abuttingly engaging and removably seating against said base and said lobes adjacent said plug, said disk defining a central axial hole for slidable receiving said handle portion and having an outer edge with a maximum span larger than said access opening but less than the maximum diameter of said symmetrical set of lobes to substantially minimize the interference with manually gripping of said manual grippable flange portions of said lobes, said disk being of a material selected from the group consisting of paper, paperboard, and plastic, and providing a removable closure member and seal for substantially closing said access opening and sealing said plug and said candy core within said shell.

The claims were rejected in view of thirteen references. The primary references, patents to Siciliano, Copeman, and Pooler, show ice cream or candy molded in a plastic, rubber or elastomeric mold. In Siciliano and Copeman the mold also serves as the product wrapper. In Siciliano the ice cream is poured into the mold, a stick [**6] is inserted, the ice cream is hardened, and a cardboard cover seals the area between the stick and the elastomeric wrapper. Copeman and Kuhlke show candy lollipops molded in elastomeric molds. Copeman states that the mold may take "varying shapes, such as in the form of fruit, or animals" and Kuhlke discusses the desirability of sealing candy from the outside air. In Siciliano, Copeman and Kuhlke, the mold is peeled from the confection prior to use.

The two Nolte patents teach that gripping flanges may be placed on an ice cream wrapper to facilitate removal. Ahern and Knaust each show a disc-shaped seal or cover for a frozen confection. Ahern shows the cover in conjunction with ice cream on a stick.

Harris shows a hollow thumb-shaped lollipop into which the thumb is inserted, and [*986] Craddock shows a thumb-shaped confection supported on a disc-shaped handle; in both cases without the other elements shown by Gorman. Fulkerson shows a candy coating surrounding a block of ice cream, and a candy plug for retaining liquid syrup inside a cavity in the ice cream. Webster shows chewing gum entirely enclosing a liquid syrup product. Spiegel shows a chocolate layer having an alcohol diffusion barrier [**7] to plug the end of a plastic container of liqueur. Fulkerson, Webster and Spiegel all suggest the greater appeal to consumers of providing two different components in the same confection.

The Board found that all of the features of Gorman's product were known to the art, and that various combinations of these elements existed in known similar structures. The Board concluded that the applicant's claimed combination was suggested by and would have been obvious in light of the references.

Discussion

A

Each element of the Gorman claims is in the prior art, separately or in sub-combination. Gorman argues that when it is necessary to combine the teachings of a large number of references in order to support a rejection for obviousness under *35 U.S.C. § 103,* this of itself weighs against a holding of obviousness.

[HN1] The criterion, however, is not the number of references, but what they would have meant to a person of ordinary skill in the field of the invention. In *Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1383, 231 U.S.P.Q. (BNA) 81, 93 (Fed. Cir. 1986), cert. denied, 480 U.S. 947, 94 L. Ed. 2d 792, 107 S. Ct. 1606 (1987),* the court held that a combination [**8] of about twenty references that "skirted all around" the claimed invention did not show obviousness. In other instances, on other facts, we have upheld reliance on a large number of references to show obviousness. Compare *In re Miller, 34 C.C.P.A. 910, 159 F.2d 756, 758-59, 72 U.S.P.Q. (BNA) 512, 514-15 (CCPA 1947)* (rejecting argument that the need for eight references for rejection supported patentability) with *Kansas Jack, Inc. v. Kuhn, 719 F.2d 1144, 1149, 219 U.S.P.Q. (BNA) 857, 860 (Fed. Cir. 1983)* (where teachings relied upon to show obviousness were repeated in a number of references, the conclusion of obviousness was strengthened). *See also, e.g., In re Troiel, 47 C.C.P.A. 795, 274 F.2d 944, 947, 124 U.S.P.Q. (BNA) 502, 504 (CCPA 1960)* (rejecting appellant's argument that combining a large number of references to show obviousness was "farfetched and illogical").

[HN2] Determination of whether a new combination of known elements would have been obvious to one of ordinary skill depends on various factors, including whether the elements exist in "analogous art", that is, art that is reasonably pertinent to the problem with which the inventor is concerned. *In re Deminski, 796 F.2d 436, 442, 230 U.S.P.Q. (BNA) 313, 315 (Fed. Cir. 1986).* [**9] When the references are all in the same or analogous fields, knowledge thereof by the hypothetical person of ordinary skill is presumed, *In re Sernaker, 702 F.2d 989, 994, 217 U.S.P.Q. (BNA) 1, 5 (Fed. Cir. 1983),* and the test is whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention. *See In re Young, 927 F.2d 588, 591, 18 U.S.P.Q.2D (BNA) 1089, 1091 (Fed. Cir. 1991).*

[HN3] When it is necessary to select elements of various teachings in order to form the claimed invention, we ascertain whether there is any suggestion or motivation in the prior art to make the selection made by the applicant. *Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 U.S.P.Q. (BNA) 543, 551 (Fed. Cir. 1985).* "'Obviousness can not be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.'" *In re Bond, 910 F.2d 831, 834, 15 U.S.P.Q.2D (BNA) 1566, 1568 (Fed. Cir. 1990)* (quoting *Carella v. Starlight Archery and Pro Line Co., 804 F.2d 135, 140, 231 U.S.P.Q. (BNA) 644, 647 (Fed. Cir. 1986)).* [**10]

The extent to which such suggestion must be explicit in, or may be fairly inferred from, the references, is decided on the facts of each case, in light of the prior [*987] art and its relationship to the applicant's invention. As in all determinations under *35 U.S.C. § 103,* the decisionmaker must bring judgment to bear. It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps. *Interconnect Planning, 774 F.2d at 1143, 227 U.S.P.Q. (BNA) at 551.* The references themselves must provide some teaching whereby the applicant's combination would have been obvious.

B

Gorman argues that the references showing ice cream in a mold or wrapper on a stick and the references showing candy in a mold or wrapper on a stick are not analogous, for they require different conditions of

production. However, the Copeman reference shows the close relationship of these arts, stating that his elastomeric mold may be used for "frozen confections and other solid confections". We conclude that the ice cream on a stick and candy on a stick arts are [**11] analogous, and that the Siciliano, Copeman, Pooler, and Kuhlke references show or suggest Gorman's candy on a stick and covered with an elastomeric mold, for which the thumb-shape is shown by Harris or Craddock.

The suggestion of providing a layer of chewing gum, chocolate or the like, surrounding the candy core in the area not covered by the mold, to seal the candy and provide a second food product, is provided by Fulkerson, Webster, or Spiegel. The paper disc adjacent the base of the candy structure is shown in Ahern and Knaust. Harris and Craddock both show thumb-shaped candy. Gorman argues that the prior art does not suggest using the thumb-shaped cover as a toy after the candy is removed. However, Copeman states that his rubber mold may be used as a "toy balloon" after the candy is removed. Gorman argues that Craddock teaches away from the claimed invention because of Craddock's admonition that lollipops on sticks are dangerous to children. However, candy on a stick is too well known for this caution to contribute to unobviousness.

Claim 16 recites details such as a "joint-shaped portion", a "finger nail portion", an "upper portion", a "lower portion" and a "convex back", as descriptive [**12] of the thumb shape. Such details are shown in the references and do not contribute to unobviousness. [HN4] A claim that is narrowly and specifically drawn must nevertheless meet the requirements of § 103:

> The mere fact that a claim recites in detail all of the features of an invention (i.e., is a "picture claim") is never, in itself, justification for the allowance of such a claim.

Manual of Patent Examining Procedure, § 706 (Rev. 6, Oct. 1987) at pp. 700-6; *In re Romito, 48 C.C.P.A. 983, 289 F.2d 518, 129 U.S.P.Q. (BNA) 359 (CCPA 1961)* (rejecting a "picture claim").

Applying the principles of *Graham v. John Deere & Co., 383 U.S. 1, 17, 148 U.S.P.Q. (BNA) 459, 467, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966),* we discern all of the elements of claim 16, used in substantially the same manner, in devices in the same field of endeavor. The various elements Gorman combined: the molded lollipop with a chewing gum plug, with the mold serving as the product wrapper; and candy in the shape of a thumb; are all shown in the cited references in various subcombinations, used in the same way, for the same purpose as in the claimed invention. The Board did not, as Gorman argues, pick and choose among isolated [**13] and inapplicable disclosures in the prior art. Rather, the claim elements appear in the prior art in the same configurations, serving the same functions, to achieve the results suggested in prior art. *In re Sernaker, 702 F.2d at 994, 217 U.S.P.Q. (BNA) at 5.* The large number of cited references does not negate the obviousness of the combination, for the prior art uses the various elements for the same purposes as they are used by appellants, making the claimed invention as a whole obvious in terms of *35 U.S.C. § 103.*

The Board's decision is

AFFIRMED.